Final Report

Cholinesterase Monitoring of Pesticide Handlers in Agriculture: 2005

Report to the Washington Department of Labor and Industries

The Scientific Advisory Committee for Cholinesterase Monitoring formed under RCW 49.17.288

January 17, 2006

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Chapter 1: Introduction

1.1 Cholinesterase Monitoring Rule Background

This report describes the 2005 operation and results of the cholinesterase monitoring program implemented by the Washington Department of Labor & Industries (L&I) under the Cholinesterase Monitoring Rule. A more detailed account of the development and history of the Rule is provided in the *Final Report - Cholinesterase Monitoring of Pesticide Handlers in Agriculture: 2004 – Report to the Washington State Department of Labor and Industries* available at http://www.lni.wa.gov/Safety/Topics/AtoZ/Cholinesterase/ files/final.pdf. The current cholinesterase monitoring rule, Chapter 296-307-148 WAC, was adopted in December 2003 and became effective in February 2004. As part of the development of the rule, the following measures were taken:

- An advisory group consisting of agriculture worker and grower representatives, other government agencies, and scientific community representatives (the "Cholinesterase Monitoring Stakeholder Group") was formed in July 2002.
- Public data-gathering meetings were conducted around the state, including representatives of small businesses that would be affected by the rule.
- L&I also provided a Small Business Economic Impact Statement (SBEIS) and Benefit-Cost Determination (BCD) as required for any rule making.

In order to accomplish a comprehensive review process, the rule requires L&I to organize a scientific team (the "Scientific Advisory Committee") to oversee collection and analysis of data collected during 2004 and 2005. The team was defined as consisting of (at a minimum) representatives from the University of Washington, Washington State University, as well as other interested members of the academic and scientific communities. In addition, L&I has organized a Cholinesterase Monitoring Stakeholder Group to evaluate rule implementation activities. Table 1.1 lists the membership of the Cholinesterase Monitoring Stakeholder Group and the Scientific Advisory Committee, as of September 2005.

The Washington Department of Health Public Health Laboratory (PHL) was chosen to conduct all testing during the 2004 and 2005 agriculture pesticide application seasons in order to ensure consistency of testing in the absence of an established laboratory testing infrastructure, and to allow efficient collection of surveillance data.

Under the Rule, testing would be open to commercial laboratories approved by L&I beginning in 2006. This has since been modified to extend the role of the PHL as the sole monitoring laboratory through 2006. The role of PHL in subsequent years has not yet been determined. (At this point in time it is L&I's intention that testing will be completely shifted to a commercial laboratory beginning in 2007.)

Table 1.1: Committee Rosters (* denotes committee consultants)

Scientific Advisory Committee	
David Kalman, PhD, Chair	Chair, Dept. of Environmental & Occupational Health Sciences, University of Washington
*Barry Wilson, PhD	Professor of Animal Science and Environmental Toxicology, University of California, Davis
*Gerald van Belle, PhD	Professor of Biostatistics and Environmental and Occupational Health Sciences, University of Washington
David Bonauto, MD	Associate Medical Director, L&I
Rupali Das, MD, MPH	Public Health Medical Officer, CA Dept. of Health Services
Allan Felsot, PhD	Professor & Extension Specialist, Entomology/Environmental Toxicology, Washington State University
Stefan Dobratz, CIH (L&I liaison)	Scientific Committee Liaison, Occupational Nurse Consultant, WISHA, L&I
Matthew Keifer, MD, MPH	Associate Professor, Depts. of Medicine & Environmental & Occupational Health Sciences, University of Washington
Michael O'Malley, MD, MPH	Associate Clinical Professor, Employee Health Services, University of California, Davis
Juliet VanEenwyk, PhD	State Epidemiologist for Non-Infectious Conditions, Washington State Dept. of Health
Cholinesterase Monitoring Stakeholder Group	
*Nathan Lacy, PhD,	Office Director for Environmental Laboratory Services, Washington State Public Health Laboratory
Allan Felsot, PhD	Professor & Extension Specialist, Entomology/Environmental Toxicology, Washington State University
Jim Jesernig	Attorney Represents potato growers
Matthew Kiefer, MD, MPH	Associate Professor, Depts. of Medicine & Environmental & Occupational Health Sciences, University of Washington
Evi Licona	Columbia Legal Services
Kirk Mayer	Washington Growers' Clearing House
Erik Nicholson	United Farm Workers
Dorothy Tibbetts	Manager, Office of Pesticide Investigation and Surveillance, WA State Dept. of Health
Ann Wick	Washington State Dept. of Agriculture, Pesticide Management
John Furman, PhD, MSN (L&I liaison)	Stakeholder Committee Liaison, WISHA, L&I

Implementation of the Rule has included the following milestones:

6/03	Selection of the WDOH PHL to conduct year 1-2 monitoring
9/03	Development of training materials for health care providers
12/03-1/04	Training sessions for health care provider
1/27/04	Beginning of 2004 baseline sample collection

3/24/04	Beginning of 2004 follow-up sample collection
9/16/04	Cut-off date in CMDS for Year 1 results to be included in 2004 analysis. This includes all samples analyzed as of 9/10/04.
10/1/04	Compiled 2004 data provided to SAC
11/12/04	Draft 2004 review provided to L&I
3/30/05	Final report covering 2004 issued
1/05 - 9/05	2005 Monitoring period
12/1/05	Draft report for 2005 provided to L&I

Charge to the Scientific Advisory Committee:

The cholinesterase monitoring rule (Chapter 296-307-148 WAC) specifically provides for a review of the experience after the first and second monitoring years in order to gain a greater knowledge and certainty about the extent and effect of overexposure to cholinesterase-inhibiting pesticides (organophosphate and N-methyl-carbamate). The Scientific Advisory Committee has been charged with overseeing collection and analysis of data, providing an initial analysis of testing data, and offering any recommendations to L&I and to the Cholinesterase Monitoring Advisory Committee by November 1, 2004 as well as a further analysis and any appropriate recommendations by December 1, 2005. A final report and recommendations will be completed by September 30, 2006. These reports will assist L&I to conduct an objective evaluation of the Rule's benefits, to make modifications, or to even repeal the rule, as appropriate. This report to L&I is the Scientific Advisory Committee's further analysis and recommendations based on 2005 data.

A primary objective for this report is to determine whether any adjustments to the program for 2006 are indicated. Examples of aspects of the monitoring program where adjustments might be made include implementation issues such as appropriate enrollment of pesticide handlers, timely and appropriate flow of information among employer, worker, heath care provider, laboratory staff, monitoring program staff, and L&I personnel such as field consultants. Responses to Committee recommendations made in the 2004 report and the effectiveness of those responses is an additional focus of inquiry.

1.2 Basis for Cholinesterase Medical Monitoring

Cholinesterase (ChE) is a family of enzymes that performs essential functions in nerve signaling between nerve cells, between nerves and glands, and between nerves and muscles, in many species from insects to humans. Without adequate ChE activity, over-stimulation and eventual exhaustion of the nerves, glands, or muscles results.

Two classes of pesticides (insecticides), the organophosphates and the N-methyl-carbamates, widely used in production agriculture, are ChE inhibitors. Pesticide handlers can be overexposed to ChE-inhibiting pesticides when breaks in worker protection protocols occur during activities such as mixing, loading, application, and maintenance of

contaminated equipment. Absorption can occur by inhalation, through the skin, by ingestion, and through the mucous membranes and eyes.

Recovery from acute poisoning occurs as ChE levels are regenerated through spontaneous reversal of the inhibiting interaction of the enzyme with organophosphate- or N-methyl carbamate components, and through the production of new ChE. For inhibition with carbamate pesticides, spontaneous reactivation of ChE can occur within a matter of hours to days. Organophosphate-related ChE inhibition may become permanent through an "aging" process; enzyme must then be replaced by new enzyme synthesis.

Except in severe cases, the treatment for pesticide-related ChE depression is to simply remove the employee from further exposure until enzyme levels regenerate. Recovery of RBC ChE occurs at a rate of slightly less than 1% per day, controlled by the rate of red blood cell production. Serum ChE is produced in the liver and regenerates more rapidly than RBC ChE. Testing to monitor serum ChE recovery may be conducted as often as weekly.

There are two types of cholinesterase in blood referred to in this report as serum ChE and red blood cell (RBC) ChE. These two categories of ChE enzymes found in blood are similar but distinct enzyme groups, with different reactivities and recovery behaviors. RBC ChE is the same cholinesterase (AChE) found in the nervous system and is thought to better reflect effects on the nervous system AChE than does serum ChE. Unlike cholinesterase enzymes found in nervous system tissues, blood ChE can be conveniently measured through carefully controlled but routine blood collection and laboratory testing methods. The use of the blood enzyme activities as markers for effects delivered to nervous system tissues is based on this similarity in form and reactivity. However, different pesticide products have different binding affinities with either RBC or serum ChE. Monitoring both RBC and serum ChE enzymes provides a more complete clinical picture of exposure.

Because there are no "universal normal" ranges established for ChE levels and wide inter-individual variation is observed in functional (baseline) levels, it is essential that each individual have baseline blood ChE levels established while free from the effect of ChE inhibiting chemicals. Generally a minimum of 30 days from last pesticide exposure and before new exposures to ChE-inhibiting pesticides is sufficient time to assure a valid baseline level. Subsequent ChE measurements are then taken on a periodic basis while the employee is handling ChE-inhibiting pesticides. These periodic test measurements are compared to an individual's baseline level in order to monitor exposure. Significant depression in ChE levels compared to the baseline indicates probable overexposure and an increased risk for developing cholinergic poisoning.

Changes in an individual's ChE levels are determined by calculating the percentage change from baseline. The State of California, the American Conference of Governmental Industrial Hygienists (ACGIH), and the World Health Organization (WHO), have established depression thresholds. California has established as significant depression thresholds 30% in RBC ChE or 40% in plasma (serum) ChE, respectively. Depressions to these levels require that the employee be removed from exposure to ChE inhibiting pesticides until levels return to within 20% of baseline. A depression of >20%

from baseline for either blood cholinesterases requires a review of the employee's pesticide handling practices in order to identify and correct any breaches in practice that are contributing to overexposure.

For a more complete description of the biological basis for pesticide exposure assessment using ChE monitoring, the reader is referred to the 2004 Monitoring report.

Chapter 2: Overview of the Cholinesterase Monitoring System

2.1 Background

The ChE monitoring system was developed as a result of WAC 296-307-148, the ChE Monitoring Rule. The ChE monitoring system flowchart, **Figure 1,** provides an overview of the 2005 system including components of the system both required and not required under the rule. A detailed description of the Cholinesterase Monitoring System is provided in the *Final Report - Cholinesterase Monitoring of Pesticide Handlers in Agriculture: 2004 – Report to the Washington State Department of Labor and Industries* available at http://www.lni.wa.gov/Safety/Topics/AtoZ/Cholinesterase/files/final.pdf. This chapter details meaningful changes to the system during the second year of rule implementation.

2.2 Enrolling Pesticide Handlers into the Program

In 2005, employers were required to refer for ChE testing handlers of toxicity class I or II organophosphate and N-methyl-carbamate pesticides meeting an exposure threshold of handling (handling includes those activities listed under the definition of "handler" in chapter 296-307-11005 WAC) 30 or more hours in any consecutive 30-day period. In 2004, the threshold was handling 50-hours in any consecutive 30-day period. The reversion to a 30-hour handling threshold was a planned program modification as provided for under chapter 296-307-14810.

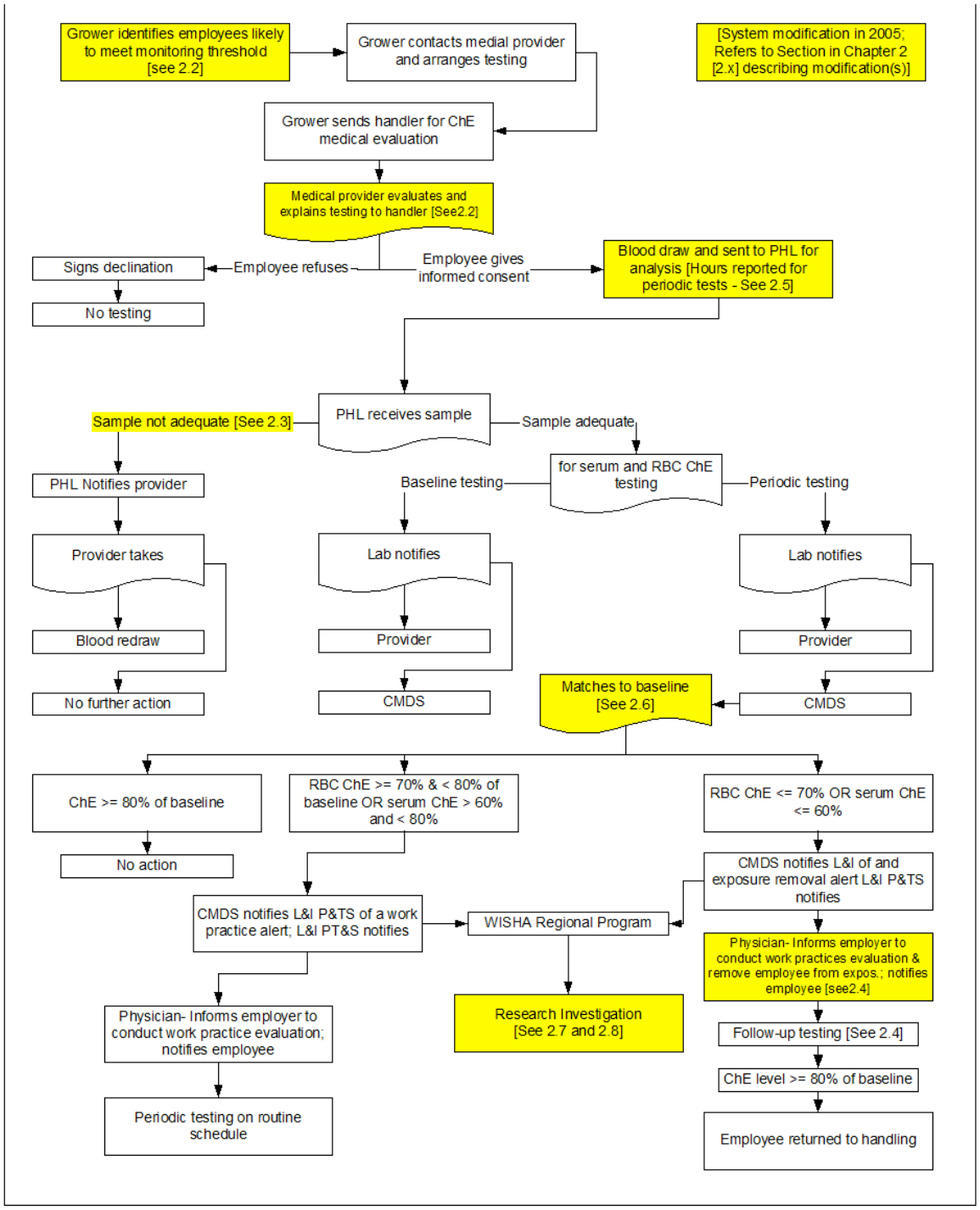
As in 2004, covered handlers were presented with the option to participate or decline participation in the testing program. The rule requires that this decision be made as part of an informed consent process with the health care provider. This implies that the worker's decision to not participate should come only after discussion with a licensed health care provider about the advantages or disadvantages of participation. L&I did not actively track the number of declinations. However, at the end of the year the health care providers conducting the bulk of the testing were surveyed regarding the number of handlers referred to them who declined testing. The results of this survey are contained in Chapter 5. The data from health care providers would not, however, provide information on compliance with medical monitoring requirements. The number of noncompliant employers (or the number of workers potentially excluded from the program) is unknown, but L&I did perform some spot testing as is discussed in Chapter 5.

In order to aid health care providers in facilitating this process, L&I adapted the UC Davis publication Jorge's New Job for use in Washington State. Copies of this publication along with the companion videotape (in both English and Spanish) were distributed to all participating health care providers.

L&I actively encouraged employers and health care providers (through mailings, training opportunities, and communication with employer representatives) to carefully evaluate the likelihood of handlers meeting the 2005 exposure threshold. This action was taken in

order to try to reduce the number of unnecessary baseline tests and to target program resources to the highest risk population. See Chapter 5 for 2004/2005 comparison data.

Figure 2.1 Cholinesterase Monitoring System Overview



2.3 Collection and Analysis of Blood Samples

Collection methods for blood samples were the same as in 2004. There was a modification of the consent form so that workers would know that L&I and the employer would have access to the test results. The Public Health Laboratory (PHL) continued as the only laboratory performing the serum (plasma) and red blood cell (RBC) ChE testing in accordance with the previously published Standard Operating Procedures (SOP) per the 2004 report. Minor modifications to the SOPs for the 2005 program are described in Chapter 3. Health care providers were notified prior to the start of 2005 testing that the PHL would rigorously adhere to the specimen rejection criteria in the SOPs.

The PHL identified the following specimen rejection criteria:

1. Specimen tube is glass, is different size than specified, or is broken or leaking,
2. Specimen is not delivered to PHL within 24-36 hours from time of collection,
3. Specimen arrives at PHL at temperature higher than 10° Celsius,
4. Specimen is hemolyzed, and
5. Minimum patient identification is not provided.

Strict adherence to the rejection criteria resulted in 146 specimens being rejected (mostly for not meeting temperature criteria) compared with only 27 in 2004. When a specimen was rejected, the PHL immediately informed the health care provider and recommended that a new sample be submitted for analysis. The PHL also advised the provider regarding shipping practices and other means to assure its receipt of valid samples.

2.4 Reporting of Results

In 2005, the PHL continued to report the results to the health care provider via mail and electronically to the Cholinesterase Monitoring Data System (CMDS) located in the Washington State Department of Health (DOH) Non-Infectious Conditions Epidemiology program. DOH electronically transferred the CMDS database to L&I on a weekly basis. DOH also provided L&I WISHA Policy and Technical Services Unit (P&TS) with a weekly report showing the workload and number of ChE depression alerts (ChE depressions >20% from a handler's baseline). Throughout 2005, P&TS continued to notify the health care provider by telephone and fax of ChE depressions greater than 20%, because CMDS often notified L&I of a depression before the provider would have received the mailed results from the PHL.

In 2005, for all ChE depressions to the exposure removal level (RBC ChE depression $\geq$30% or serum ChE depression $\geq$40%), P&TS asked health care providers to verify that they had contacted the employer and instructed that the handler be removed from exposure to covered pesticides pending ChE recovery. In addition, P&TS ensured that the health care provider had scheduled handler follow-up testing. Field research investigations were then initiated after P&TS verification of employer notification (usually that same day).

2.5 Reporting of Handling Hours

RCW 49.17.285 requires that employers report to the health care provider and approved laboratory pesticide handling hours for the 30-day period immediately prior to testing and total hours for the year. This was accomplished through the use of a required handling hours report form (L&I form F413-065-000). The employer submitted this form to the health care provider who included it with the test requisition form submitted to the PHL. The PHL added test identification numbers and sent the forms to L&I to match with tests and add handling hours data to the L&I test database.

2.6 Baseline and Periodic Testing

Requirements for baseline and periodic testing were identical to those in 2004 except that the threshold was changed from handling covered pesticides for 50 to 30 hours in 30 consecutive days. This change is consistent with the requirements in the ChE Monitoring Rule, Section 296-307-14810. Changes from baseline were calculated in the same manner in 2005 as in 2004: {((baseline result – periodic result)/baseline result) x 100}.

As in 2004, CMDS's matching routine for baseline and periodic tests used probabilistic matching software (Netrics). The matching algorithms were the same in 2004 and 2005 except that place of birth was not collected in 2005, because this field proved not useful for matching in 2004. The match used handlers' first, middle and last names, date of birth, race/ethnicity, and mother's surname. The process of manual matching was more efficient in 2005 than in 2004 because of the addition of a comments field for suspended records (records with indeterminate matches). When the CMDS operator contacted the provider or employer to acquire additional information to resolve an indeterminate match, she was able to use the comments field to track resolution. Comments were easily viewed in suspended records, reducing duplication of work and eliminating the inefficiency of paper tracking.

In 2004, approximately 65% of periodic tests needed manual review for matching to baseline. In 2005, about 50% required manual review. This reduction is most likely a combination of more complete reporting and narrowing the range of probabilities for manual checking. This time-consuming process could be improved by the issuance of unique identifiers to participating workers. Such a modification is likely to be more important in the future when the program is self-supporting and resources for program evaluation become scarce.

2.7 Work Practice and Workplace Removal Alerts

As specified by the Cholinesterase Monitoring Rule and described in the 2004 report, the system for issuing "work practice evaluation alerts" and "exposure removal alerts" was the same in 2004 and 2005. As noted above, when CMDS issued an alert, WISHA P&TS notified the health care provider. WISHA also conducted research investigations to evaluate pesticide handling and worker protection programs in accordance with WISHA

Regional Directive (WRD) 33.27 (http://www.lni.wa.gov/Safety/Rules/Policies/PDFs/WRD3327.pdf). Upon being notified of a work practice evaluation or exposure removal alert, the L&I research investigator scheduled a site visit with the employer, which also included an interview with the affected handler. Research investigations were conducted for all but one of the 28 employers with a handler with ChE depression to the work practice evaluation or exposure removal level. (That one exception was referred to L&I compliance program for follow-up, following repeated failures of the employer to schedule a site visit.)

2.8 WISHA Research Investigations

When P&TS notified the health care provider of a periodic test result requiring exposure removal or a work practice evaluation, they instructed the health care provider to inform the employer of the event. Subsequently, the provider was to confirm with P&TS this communication for all ChE depressions to the exposure removal level. P&TS then notified the WISHA ChE monitoring research investigator. The same research investigator conducted all but one of the ChE field investigations. WISHA research investigations collected information utilizing a standard series of questions (see WRD 33.27). The questions included worker name, birth date, primary language, and number of years as a handler. The employer name was recorded along with additional information regarding the number of acres, crop types, the types of ChE inhibiting pesticides handled, the number of handling hours, handler training, types of pesticide handling activities, use of personal protective equipment (PPE), decontamination facilities, handler symptom history, and identification of the potential cause of exposure. The investigator summarized the reports for use by the scientific advisory committee.

2.9 Summary of Roles and Responsibilities

As initially presented in the 2004 report, the roles and responsibilities for the employer, health care provider, the Department of Health, and the Department of Labor and Industries as specified in WAC 296-307-148, the Guidelines for Health Care Providers, or the PHL's Standard Operating Procedures remained intact for the 2005 season. The few changes for the 2005 season include:

1. The health care provider sending the Cholinesterase Monitoring Handling Hours report to the Public Health Lab with the test requisition,
2. The health care provider obtaining written authorization from participating handlers to share test results with the employer,
3. L&I P&TS verifying that physicians notified the employer of the worker with a ChE depression to the exposure removal level and coordinating a schedule for follow-up monitoring of these handlers,
4. Use of a 30-hour exposure threshold prompting employers to refer handlers for medical evaluation and testing,

5. Dedication of a single research investigator from L&I to conduct worksite visits for ChE depressions meeting criteria for a work practice evaluation or exposure removal.

Information surfaced during both the 2004 and 2005 seasons that handlers who did not have ChE alerts were not receiving their ChE monitoring test results in a timely fashion, if at all. Failure to notify the handler of the test results for ChE monitoring could potentially result in less handler participation in the ChE monitoring program. The present (2004/05) ChE monitoring system relied on the Public Health Laboratory to notify the health care provider of the ChE monitoring results. The health care provider is responsible for notifying the employer of ChE depressions requiring action. The rule originally assumed that the worker would be informed of test results through common physician/patient communication channels. There was in 2004 and 2005 no requirement for the employer, L&I, CMDS, or the public health laboratory to routinely notify the handlers of his/her test results. The rule did require the employer to provide test results and other documentation to the employee or his or her designated representative upon request, and as modified 12/20/05 now requires employers to ensure that employees receive copies of health care providers' reports for every test including baseline. As a medical standard of care, notification of a patient's laboratory test results is incumbent upon the health care provider, and this approach is preferred by both labor and grower representatives on the Stakeholders Advisory Committee. There remains a question regarding sole reliance on health care providers to compare test results, detect depressions, and initiate and communicate alerts, particularly under the current monitoring system data flow, in which L&I is aware of an alert-level depression before the health care provider would be. When or whether L&I staff would cease to provide independent notification of alerts to heath care providers or employers is still not determined.

2.10 Potential Future Changes

The committee notes that major changes are planned for the system in the next couple of years. These changes include contracting with a private laboratory for ChE testing, discontinuation of L&I subsidizing ChE laboratory testing and program maintenance expenses, and significant potential disruption in the assistance provided by state agencies to data flow for the ChE monitoring system. The Scientific Advisory Committee suggests that L&I have extensive interaction with both the SAC and the Cholinesterase Monitoring Stakeholder Group in managing the upcoming transition.

Chapter 3: Data Quality

This chapter evaluates the quality of 2005 monitoring data. The prior report to the Washington State Department of Labor and Industries (L&I), "Cholinesterase Monitoring of Pesticide Handlers in Agriculture: 2004" provides a basic discussion of quality control concepts and their application to the measurement of ChE depression.

3.1. Methods and practices

The 2004 evaluation of data quality identified several key issues regarding data quality.

- Timeliness of sample analysis and reporting was a significant problem. Delays were caused by method adjustments combined with unexpectedly high sample submission rates early in 2004.
- Lab capacity needed to be increased so that sample holding time requirements could be met.
- Precision (how reproducible a measurement is) was within the norm for standard lab practices, but was lower than needed for monitoring program goals.
- Bias (systemic factors effecting test results e.g., storage times, variation in sample preparation) was a major source of uncertainty, especially for RBC. An unexplained pattern of RBC ChE activity increases was seen over the 2004 monitoring season. This led to questions about overall data reliability.
- Acceptance criteria for samples needed more stringent application.
- The procedures used for QC review needed more specification and documentation.
- External QC data (from samples submitted blind to the lab) were key, and needed expanded use.

Response to 2004 recommendations

The Departments of Health and Labor & Industries responded to each lab-related recommendation from the 2004 Report. Many of the recommendations were adopted, as follows:

- Revisions to SOP: the PHL Standard Operating Procedure for this activity was completely revised for 2005 monitoring. Key changes included: revised specifications for sample collection and shipping; criteria for rejecting samples upon receipt; replacement of –20°C storage with –70°C storage for samples prior to and following analysis and for calibrants and other QC samples; further optimization of instrument operating parameters (reduced sample volumes); increased numbers of QC samples and increased specification and tighter limits for QC procedures; addition of hemoglobin determination in RBC ChE tests.
- Increase of lab capacity: prior to the start of 2005 monitoring, a second Dade AR analyzer and -70ºC freezer were added to the PHL, effectively doubling the

instrumental analysis capacity, providing backup capability in the event of an analyzer malfunction, and greatly expanding low temperature storage.

- Rejection of compromised samples: The new and more detailed criteria for sample rejection included in the 2005 SOP revision was followed rigorously in 2005, with increased numbers of samples being rejected for non-conformity with collection or shipping SOP requirements compared with rejections in 2004. These mainly occurred at the start of the monitoring period, and the PHL actively worked with health care providers to correct procedural deficiencies.
- Continue blind QC: L&I organized and maintained the blind external QC program throughout the period from January through September 2005. A total of 377 external QC samples were submitted to the PHL over 7 submission cycles.
- Hemoglobin determination: The 2004 report recommended that the PHL consider incorporating hemoglobin measurement in the analysis protocol for every sample. With the purchase of a new hemoglobinometer, this was done on a pilot basis in 2005, with the data being provided to the SAC.
- Review overall protocols: Dr. Nathan Lacey of the PHL visited the laboratory of Dr. Barry Wilson at UC Davis in order to gain additional expertise in this measurement and to identify opportunities to improve the assay. Some of these were implemented in 2005, while other changes await a determination of the long-term plan for a support lab for this program.

Some recommendations and identified issues remain unresolved:

- The suggestion was made that a formal QC checklist be developed and used as part of data validation. It is not clear whether this has been adopted. Review of the full data package for a few random samples indicated that QC reviews included notations on the auto-analyzer report sheets, but no QC checklist was provided.

Some issues and recommendations requiring substantial development time were deferred because of the uncertain future of this program at the PHL:

- The use of multiple enzyme substrates with the Dade auto-analyzer to independently optimize instrument response for RBC and serum ChE,
- The need for a reference material for routine use for RBC ChE assay benchmarking,
- Conducting sample exchanges and interlab comparisons with other labs doing ChE measurement,
- Considering the feasibility and merit of incorporating multiple baseline samples and/or confirmatory analyses.

- The capability to transmit auto-analyzer data to the lab data network so that QC data could be easily compiled without hand transcription was lost when the data link was severed in July 2005.

3.2 Year 2005 Experience

Capacity: Despite the lowering of the number of hours of pesticide handling needed to bring workers under the ChE Monitoring Rule from 50 hours/month to 30 hours/month the number of samples remained comparable to those seen in 2004. The expanded laboratory capacity for 2005 was sufficient to manage incoming samples.

Timeliness: In 2005, all samples were processed and assayed within the period stated in the SOP. During the startup months when sample submissions were at their peak, there was some backup in reporting out of routine baseline results. The reporting backlog peaked in the week of March 20 (~1250 backlogged tests) but was reduced to fewer than 100 tests by early May. This condition did not affect any notifications of periodic test results.

Samples Acceptance: As noted, criteria for sample rejection based on packaging, containers used, shipment temperature, sample volume, sample appearance, or integrity were carefully defined and rigorously applied. This resulted in an increased number of rejected samples early in the monitoring period, but improved as the health care providers became more familiar with the requirements and precautions needed. Only 7 periodic test samples were rejected during 2005.

Data Completeness: Greater than 99% of all accepted samples were successfully assayed and reported.

Adherence to Assay Protocols: This was assessed by review of documentation for a random sample of submissions and results. Although the lack of a specific QC checklist was noted, the materials provided indicate that the SOP was being followed and that data were scrutinized for quality control indicators as part of the analysis process.

3.3 Evaluation of 2005 QC Data

Quality control data considered for 2005 were of the same sort as was reviewed in 2004. QC data generated within the PHL consisted of instrument report sheets, batch report sheets, control charts and compilations of control sample results. External QC data were obtained and statistically evaluated by L&I through submission of blind (disguised) QC replicate samples. In addition, some aspects of data quality can be derived from actual monitoring results.

Precision of Monitoring Data

Most of the QC data described above are useful as indicators of data precision. These are summarized in Table 3.1, below. Precision is quantified using the parameter "coefficient of variation" or %CV, which is calculated from the standard deviation of a data set divided by its average value. %CV is therefore a measure of proportionate error.

Table 3.1: QC summary, precision		estimated %CV 2004		estimated %CV 2005	
Data considered	Sources of variation included	RBC	serum	RBC	serum
Duplicate measurements	Instrumental precision only	1.3%	0.5%	0.6% (sample)	0.5% (sample)
Lab duplicates	Within-batch assay precision	4.9%	**8.3%	4.0%	1.4 %
QC control samples	Assay precision over time	6.4%	~ 4 %	5%	3 to 5%
Blind field replicates	Within-batch assay precision[1]	6.5%	1.6%	4.2%	2.1%
Repeated samples	Assay precision over time + storage effects	12.6%	8.3%	**Not Applicable**	
*Monitoring results	Assay+sampling precision + within-person variation	9%	10%	5.5%	6.6%

* These findings are discussed in Section 4 of this report.; ** exclusion of 1 of 27 pairs of lab duplicates reduces this %CV to 1.1% ***based on a 25% sub sample (1 week/month); N = 122 replicate pairs

Table 3.1 compiles the available QC performance parameters related to assay variability. The first three of these are from within lab QC measurements. Duplicate measurements are made at the instrument for every sample run. This statistic was obtained from a random sample of 30 assays and reflects the precision of the optical measurement of a single assay, and is a small component of overall assay variability. Lab duplicates are in-lab replicate preparations and analysis, and therefore reflect more of the variability of real samples than do duplicate instrument readings of a single preparation.. These results are included in each batch of samples and are reviewed within the batch report as part of the ongoing data validation process, but were not compiled in an electronic form across the 2005 monitoring period. For this evaluation, a subset of these data consisting of the first week of results each month were compiled electronically and resulted in the 4%CV (RBC) and 1.4% CV (serum) indicated. These numbers show substantial improvement over the corresponding 2004 values.

[1] Overall variation among 53 pairs of replicated samples expressed as a coefficient of variation is calculated as shown in Appendix 1

Reproducibility tends to be better for duplicate samples (run at the same time) compared to repeated samples run at different times. When samples are run with intervals of weeks or even months in between, a number of sources of variation that don't apply to same-day measurements can become significant: calibration, long-term instrument performance, changes in personnel or minor changes in practices or procedures. These factors are better assessed using a long-term "benchmark" control sample. The PHL uses 4 such control samples, which are run with every batch or tray of actual samples. For the period 1/13/05 to 9/20/05, the PHL compiled some 338 measured results for one of these control samples ("HR RBC") and made over 200 measurements of each of two others. The %CV calculated from the average and standard deviations of these data range from ±3% of the mean to ±5% of the mean among the 4 materials. This index of performance is comparable to or slightly better than the equivalent statistic from 2004.

In 2005, L&I conducted blind field QC testing throughout the monitoring season, as was recommended by the SAC. Beginning with an initial pool of some 50 volunteers comprised of either L&I staff or health care provider staff. Samples were submitted to PHL in duplicate monthly over 7 months, disguised as pesticide handler samples. Duplicates were given different identities. The detailed report on these data may be found in Appendix A. Replicate precision values across the 7-month period were 4.1 %CV for RBC ChE and 2.1 %CV for serum ChE. The serum values are comparable and the RBC values better than the equivalent parameters from 2004.

In 2004, a significant number of samples were re-assayed because excessive holding times and concern about overall RBC assay validity raised questions about the original measurement. The variation between these repeated measurements and the initial ones was larger than would have been predicted by assay performance alone, but it was not possible to differentiate analysis improvements or changes from to the samples during storage. In 2005, these issues did not arise due to prompt analysis and expanded lab capacity that avoided a backlog of samples awaiting analysis. There was no repeat analysis of stored samples.

In addition to all of the measures of assay precision from QC efforts, analysis of the monitoring data themselves yields an estimate of within-person variability. From the 2004 analysis, these results were 8.8 %CV for RBC and 9.5 %CV for serum ChE. In 2005, a comparable analysis produced values of 5.5 %CV for RBC and 6.6 %CV for serum ChE. These findings are not derived from QC data but are consistent with QC results. In the discussion of the impact of measurement or other analytical error on monitoring program alerts presented in the following chapter, the precision of each assay is characterized as 6 %CV and 7 %CV (RBC and serum, respectively), as being consistent with both lab and field QC data and conservative (less favorable than the other measures cited in Table 3.1)

Accuracy of Monitoring Data

The issue of establishing measurement accuracy is discussed fully in the 2004 Report. The PHL in April and July 2005 successfully participated in interlaboratory testing

conducted by the College of American Pathologists. This program tests assays of serum (butyl) ChE and the PHL results were well within acceptance limits. The other principal method for assessing bias for 2005 monitoring data remains the comparison of PHL results with manufacturers' certified values for those reference materials that are available and were analyzed on an ongoing basis. Unfortunately, these are also reflective of serum (butyl) ChE, and not as applicable to RBC ChE samples or AChE. Comparing several of these materials between manufacturer's reference ranges with the control limits established by PHL from statistical analysis of its own data (shown in Figure 3.1) indicates that the PHL assay is considerably more precise than the manufacturer reference range, and that the bias (indicated by differences in mean values between manufacturer and PHL) is small. Only one material exceeds 2.2%, and that is a recently-adopted new material for which the number of PHL measurements is small ("Precinorm U," 39 measurements versus 187 for the previous version of this material). Therefore, for the serum assay, it is unlikely that there is a significant bias effect.

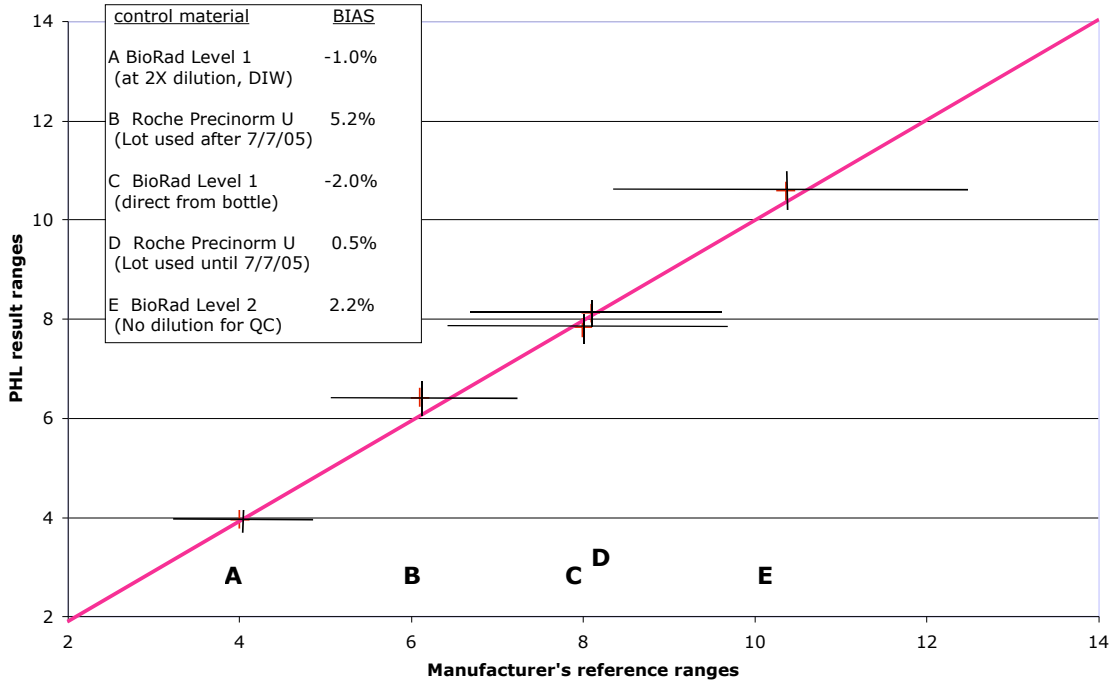


Figure 3.1 Bias and Precision in Measurements of (serum) ChE Control Materials

The RBC assay remains difficult to compare across laboratories. Establishing comparability for changes in RBC ChE level across laboratories remains a key need of this program. A control material was developed by the PHL to serve as a benchmark of assay response, but this material does not have any established values from outside of the PHL lab. Inspection of control charts for this material indicate a downward trend in values over the period 1/13/05 – 5/5/05, amounting to some 10% of the initial activity. This could indicate loss of activity in the benchmark sample or drift in the assay, but either way underscores the need for stable and well-validated RBC ChE control

materials. If this trend were indicative of assay bias and applicable to actual samples, it would tend to increase the number of alerts (early baseline values being elevated relative to later periodic values). The actual small number of RBC alerts seen in 2005 would suggest that this artifact either doesn't occur or is a small effect.

3.4 **Summary and implications**

Across several measures of analytical performance, the PHL in 2005 demonstrated improved reliability of measurement. This improvement was accomplished through expanding resources and lab capacity, through continued attention to control of the sampling and measurement process, and through continued development of methods and experience with this assay. The PHL is to be congratulated on this progress and is encouraged to maintain the procedural and organizational improvements.

Precision and Accuracy

The Science Advisory Committee notes significant improvement over 2004 by nearly every measure, for both RBC and serum ChE. There was good consistency among measures of precision. RBC still appears more variable than serum by most measures, but less so than in 2004. External QC and within lab QC are in excellent agreement, implying that within lab measures are not biased

Accuracy remains harder to assess than precision, especially for RBC ChE. Test results for control materials show good accuracy (little bias), but assessment of accuracy through use of control materials is complete for serum ChE only. Baseline activities were comparable for workers with and without alerts for serum ChE, indicating that the two groups did not differ at baseline due to laboratory bias or some other artifact.

Remaining needs and recommendations:

Some analysis modifications recommended in 2004 were not attempted because of uncertainty over future role of PHL in this program. Determining the longer-term role of the PHL in this monitoring program is highly desirable if the lab is to make strategic plans to develop this assay further.

Inter-lab exchanges and development of a robust control material for RCB ChE is still needed. The possibility of false negative results (those which indicate depressions of less than alert levels when the true value would indicate depressions above alert levels) cannot be addressed directly, but continued improvement in precision and accuracy should reduce both false negative and false positive (that is, results indicating alert-level depression when the true value would indicate depressions below alert levels) alerts.

Subsequent chapters will include discussion of the benefit of multiple baseline samples to reduce false positive alerts, and issues that would arise if the monitoring effort were to be moved to a new laboratory.

Chapter 4: Analysis of 2005 Cholinesterase Monitoring Data

This section describes the results of the analysis of the ChE monitoring data collected on handlers participating in the state monitoring program. The data were obtained from the L&I after the agency supplemented the CMDS database originally assembled by the Department of Health (DOH). The database included the results of the ChE tests, demographic information, and the number of hours worked as reported by the employer and linked to the specific test (or subject). The data were provided to the committee from L&I in the form of an Excel spreadsheet.

A more complete description of the structure of the data set and general characteristics and an analysis of the 2004 monitoring program and results can be found in the report: *Cholinesterase Monitoring of Pesticide Handlers in Agriculture: 2004 Report to the Washington Department of Labor and Industries.*

Data analysis issues from 2004 included misidentification of some individuals as pesticide handlers who submitted samples but did not fall under the ChE monitoring rule. These extraneous results were eventually excluded from the final analysis, to the best of the SAC's knowledge. This problem did not recur in 2005. Identification of the initial sample as "baseline" or "working baseline" was problematic in several cases because of discrepant information provided in the sample submission sheet. For example, classification of a sample as "baseline or "working baseline" was sometimes inconsistent with the reporting of hours of pesticide handling during the 30 days prior to the baseline test. Were significant ChE depression to be present at baseline sampling but not realized, that would pose a problem for interpreting the monitoring findings, reduce the protection afforded to that worker, and potentially inappropriately undermine confidence in testing results. Other aspects of data management and reporting are addressed in Chapter 5 of this report.

4.1 Number of Workers Tested

The numbers of workers with valid tests for baseline enzyme activity and periodic monitoring are shown in Table 4.1. The average enzyme activities for the whole population of workers tested at each interval are also included. Of the total workers tested for baseline enzyme activity, 2246 had a valid red blood cell (RBC) test, and 2256 had a valid serum test. This analysis did not investigate the reasons for fewer successful RBC analyses, but the RBC results represent better than 99.2% data completeness.

Table 4.1 – Average red blood cell (RBC) ChE and serum ChE enzyme activity in workers tested at baseline and over six periodic tests.

	Base line	Periodic Test Number					
		1	2	3	4	5	6
RBC ChE Analysis							
Number of workers tested	2246	611	203	103	25	8	4
Average activity	11.4	11.2	11.0	11.2	11.0	11.2	11.6
95% Confidence Interval	11.3–11.4	11.1–11.3	10.9–11.2	11.0–11.4	10.7–11.3	10.9–11.3	11.3–12.0
Serum ChE Analysis							
Number of workers tested	2256	611	203	103	25	8	4
Average activity	4.6	4.4	4.1	4.1	3.9	4.0	4.0
95% Confidence Interval	4.6–4.7	4.3–4.5	4.0–4.2	4.0–4.3	3.5–4.2	3.5–4.4	3.3–4.7

Of the total number of workers providing a baseline blood sample, 611 also provided at least one periodic sample. It should be noted that "periodic test number" is the sequence of testing for each pesticide handler and is not defined by the date of sample collection. Some workers were having a 6th periodic test while others were having a first periodic test. Thus, over the growing season a total of 611 pesticide handlers were tested, but the numbers undergoing subsequent repeated periodic testing decreased as the growing season progressed (Table 4.1). Altogether, 904 blood samples were collected over a maximum of six periodic tests. These quantities are comparable to those seen in 2004, during which 2655 baseline and 911 periodic tests were completed.

4.2 Demographic Information

The CMDS database recorded a total of 3217 tests for RBC and serum ChE during the 2005 monitoring season. The total number of tests includes baseline or working baseline enzyme activity monitoring on 2263 workers. The average age of pesticide handlers who were tested was 36.0 ± 9.6 years and ranged from 16 – 71 years. Among pesticide handlers with at least one periodic test, the average age was 34.9 ± 8.7 years and ranged from 16-64 years. Nearly all the handlers were male (99.5%) of Latino/Hispanic ethnicity (93% of all handlers and 97% of handlers with periodic tests). The pesticide handler population shows similar overall characteristics to that seen in 2004, and roughly half (about 1150 of the 2263) are in fact the same individuals. Additional detail for the 2004 monitoring season can be found in the 2004 report.

4.3 Working baselines and the effect of prior pesticide handling hours

"Working baseline" is the term given to a baseline samples that were obtained after pesticide handling had commenced, either because of late classification of a pesticide handler under the ChE Monitoring Rule, or because the original baseline sample was compromised in collection or analysis. At the time of baseline sample collection, pesticide handlers responded to questions on the sample submission form that asked whether the sample was a working baseline or a true baseline and, separately, how many hours of pesticide handling had occurred during the prior month. Some handlers reported 1 or more hours of pesticide use at baseline (but did not identify their initial sample as a working baseline). Evaluation of these cases determined that there were several instances of the reported handling hours being erroneous, but baseline samples were retroactively reclassified as working baselines in 16 instances. There were also 11 instances where it could not be readily determined whether the baseline sample was a true baseline or a working baseline. Modification of the sample submission form and/or improved provider training to avoid this confusion in the future is recommended.

According to the guidelines for participating in the ChE monitoring program, pesticide handlers were supposed to have taken an initial blood test prior to working with any covered insecticides. However, the database indicated that 165 handlers (or 7.3% of the total workers) had already worked with the products by the time they were tested. Forty-eight of those workers associated with handling hours at baseline testing received periodic tests. Thus 7.9% of the workers with periodic tests had already worked with covered insecticides sometime within the 30 days prior to submitting a baseline test. For most of the subsequent analyses, these handlers were included among the 611 total workers with periodic tests after baseline testing.

Baseline RBC and serum ChE activity levels did not differ significantly between the handlers who submitted only baseline tests and those that underwent at least one periodic test. However, on average both RBC and serum baseline enzyme activities were slightly but statistically lower among handlers who reported working with pesticides covered by the ChE Rule within 30 days prior to baseline testing when compared to those who reported no hours of exposure prior to baseline testing (Table 4.2). This observation applies to all comparisons in serum ChE activity: for all handlers, for those only submitting a baseline test, and for those with at least one periodic test. RBC ChE tests were statistically different when all handlers and those with only a baseline test were compared. No significant difference was observed in the RBC enzyme activity from handlers with periodic tests (Table 4.2).

Table 4.2. Mean RBC and serum ChE activity among all pesticide handlers and those undergoing only baseline and periodic tests. Handlers were classified by whether they reported handling covered insecticides within 30 days of testing ("Working Baseline") or they had not reported hours during that time frame ("Baseline").

Worker Category	Baseline Enzyme Activity (n=# workers)	95% Confidence Interval	Working BL Enzyme Activity (n=# workers)	95% Confidence Interval
RBC ChE Activity				
All workers	11.42 (2082	11.37–11.47	11.10 (164)	10.90–11.30
All Workers with Baseline Test Only	11.42 (1519	11.36–11.48	11.06 (116)	10.79–11.32
All Workers with Periodic Tests	11.41 (563)	11.32–11.51	11.20 (48)	10.94–11.46
Serum ChE Activity				
All workers	4.66 (2091	4.62–4.69	4.34 (165)	4.22–4.47
All Workers with Baseline Test Only	4.65 (1528	4.61–4.69	4.41 (117)	4.27–4.56
All Workers with Periodic Tests	4.69 (563)	4.62–4.75	4.18 (48)	3.96–4.39

4.4 Testing Frequency Relative to Time of Year

The first baseline tests were submitted in January and a few were submitted as late as July during 2005. The majority of baseline tests were submitted in February and March (Table 4.3, Figure 4.1). The majority of periodic tests were submitted during April followed by May. The pattern of blood sample submittals corresponded to the use of covered insecticides during a time when fruit trees are in dormancy or have very little canopy.

Table 4.3. Monthly blood samples submitted during crop year 2005.

Month	Baseline		Periodic Test Number					
	All Workers	Workers with Periodic Test(s)	P1	P2	P3	P4	P5	P6
Total # of Tests	2263	611	611	203	103	25	8	4
January	68	6	0	0	0	0	0	0
February	883	244	0	0	0	0	0	0
March	1064	312	98	0	0	0	0	0
April	113	31	312	6	1	0	0	0
May	91	6	73	83	12	4	1	0
June	23	12	98	61	36	4	3	2
July	23	0	18	28	31	11	1	0
August	0	0	12	24	23	6	3	2

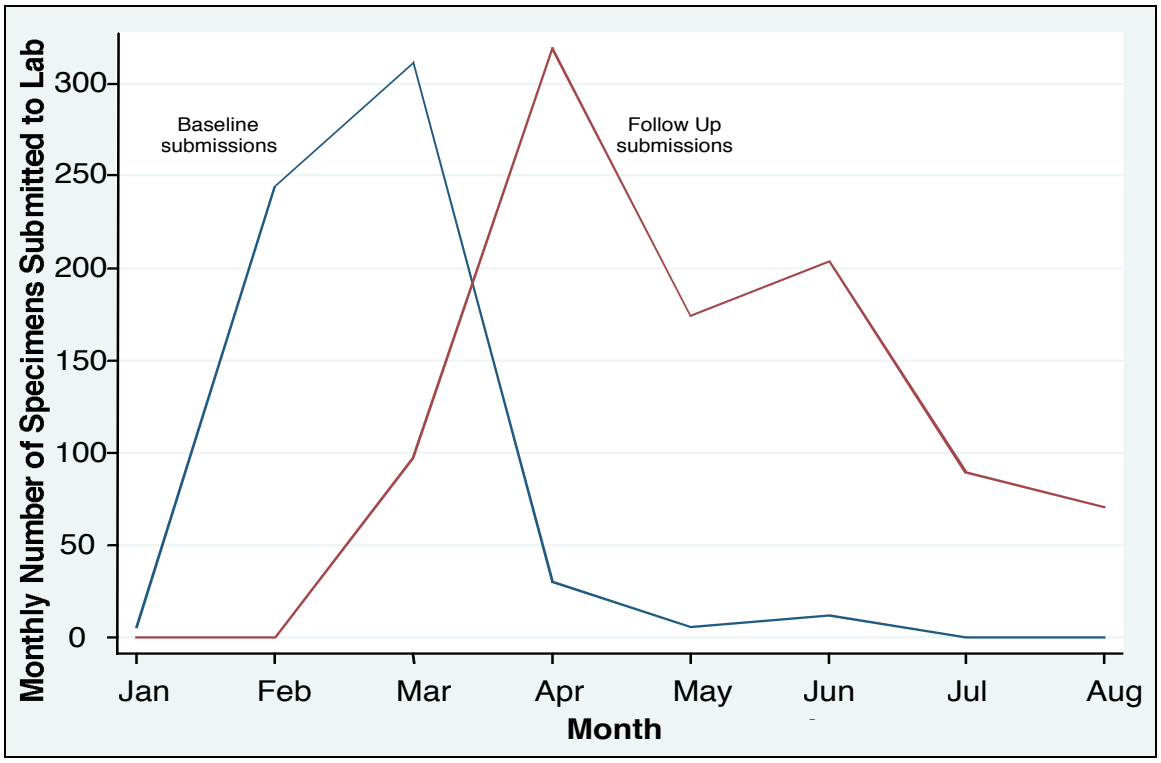


Figure 4.1. Monthly receipt of blood samples by the DOH Public Health Lab during 2005. All samples are from handlers with at least one periodic test (P1, P2, etc.)

4.5 Comparison of 2004 and 2005 Enzyme Activity Baseline Levels

L&I matched the Handler ID codes assigned during 2004 with those from 2005. Thus, it was possible to compare baseline enzyme activity to determine how some workers varied from 2004 to 2005 and how populations of workers might vary from year to year generally.

For RBC comparison, 1153 workers with paired data were evaluated. The average RBC ChE activity was 11.48 units in 2005 and 12.22 units in 2004. Comparing each handler's 2004 baseline value with the corresponding 2005 baseline value gave a difference that ranged from –8 to +4 activity units, but averaged –0.74 activity units. These averages were statistically different according an analysis using a standard t test. Cases showing lower RBC ChE activity in 2005 versus in 2004 outnumbered cases showing higher RBC ChE levels in 2005 over 2004 by 818 to 328, 71% of cases showed lower activity in 2005. The difference can be visualized in a scatter graph of enzyme activity for 2005 plotted relative to activity measured in 2004 (Figure 4.2). Note that the aggregation of symbols tends to be below the diagonal line, indicating that the average is higher in 2004. In addition, the correlation between 2005 and 2004 RBC ChE activity within individuals was poor (correlation coefficient = 0.4).

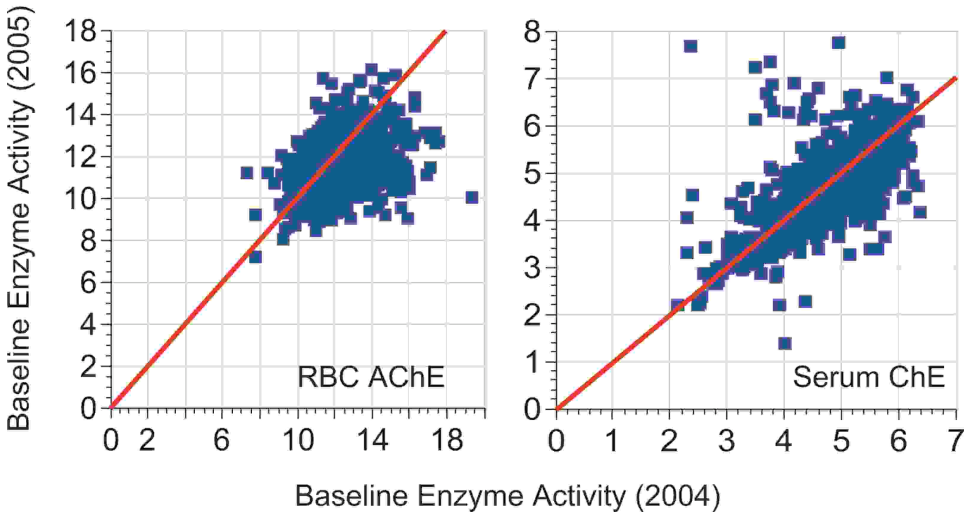


Figure 4.2. Comparison of baseline enzyme activity in blood samples collected during 2004 and 2005. The line is the ideal model in which a worker's baseline enzyme activity in both years would be exactly the same.

Similar comparisons were made for serum ChE activity on the 1138 valid paired tests. The average serum ChE level was 4.68 during 2005 and 4.73 during 2004, with cases showing higher levels in 2004 exceeding cases showing higher levels in 2005 by 657 to 476, 58% of cases. According to the "t test" analysis, serum ChE levels were significantly different between years, although the difference was less than that observed for RBC measurements. Figure 4.2 panel B shows much more variability in the RBC data but much less high or low trend between years. The correlation between 2004 and 2005 serum ChE levels was much stronger (correlation coefficient = 0.7).

At this point, these differences in activity levels between years are too small to make any conclusions regarding periodic tests, and generally are consistent with improvements in data quality seen in 2005 for RBC ChE over that in 2004. The caveat with this analysis is that it is conducted over the whole population and thus cannot be used to state how an individual's enzyme activity varied between the two years nor predict what it might be the next time it is measured.

4.6 Changes in ChE Activity During 2005

Among the 611 pesticide handlers providing at least one periodic blood sample, percentage change in enzyme activity could either be elevated (i.e. more negative in value) or depressed (i.e. more positive in value) relative to the baseline activity (Figure 4.3).

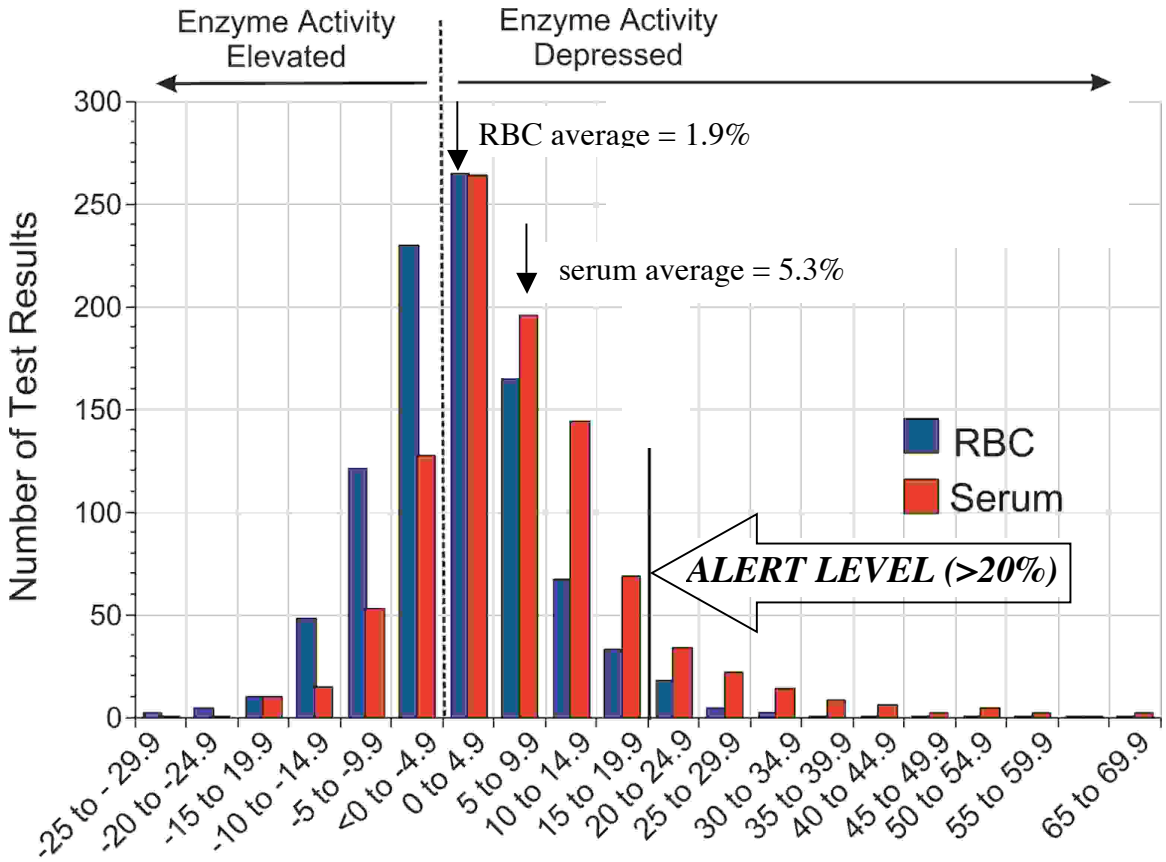


Figure 4.3. Frequency distribution of RBC and serum enzyme activity in categories of percentage decrease from baseline levels.

Enzyme activity levels were grouped into categories of 5% change and worker RBC and serum tests assigned to each category. In general, both types of enzymes exhibited a normal distribution in percentage change. Both RBC ChE and serum ChE showed a shift towards depression on average on the first periodic test representing a statistically significant decrease in both enzymes when comparing periodic test one to baselines. This effect was even more evident when subjects who reported pre-baseline exposure were removed from the analysis under the assumption (as demonstrated in Table 4.1) that some biological depression was already present at "baseline" for that group.

4.7 Alerts and Work Removals Analysis

Workers had up to six periodic tests during the period from March-August 2005. A first periodic test for RBC ChE and serum ChE was given to 610 and 611 workers, respectively (Table 4.4, 4.5). The proportion of workers taking more than one periodic test diminished by 25%-50% with each subsequent test.

Table 4.4. Numbers of periodic tests, worker alerts based on an RBC ChE depression >20% of baseline, and work removals based on depression > 30% of baseline.

Variable	Periodic Test Number						Total
	1	2	3	4	5	6	
Total Number of Tests	610	203	103	25	8	4	953
Number of Alerts	10	9	1	1	0	0	21
First Time Alerts	10	5	0	1	0	0	16
Number of Removals	1	0	0	0	0	0	1

Table 4.5. Numbers of periodic tests, worker alerts based on serum ChE depression >20% of baseline, and work removals based on depression > 40% of baseline.

Variable	Periodic Test Number						Total
	1	2	3	4	5	6	
Total Number of Tests	611	203	103	25	8	4	954
Number of Alerts	30	27	17	9	2	1	86
First Time Alerts	30	16	1	1	0	0	48
Number of Removals	6	4	1	1	0	0	12

Throughout the whole monitoring season, there were a total of 59 handlers with ChE depression >20% from baseline. Of these, there were 49 handlers with ChE depression at the work practice evaluation level (37 with serum depression, 10 with RBC depression, and 2 with both RBC and serum depression), and10 handlers with ChE depression to the exposure removal level (9 with serum depression, 1 with RBC depression). The proportion of work practice alerts for workers having one or more periodic tests was 2.6% for RBC ChE and 7.9% for serum ChE, while exposure removal alerts from either ChE test affected 1.6% of all workers with periodic testing.

A significant number of workers had multiple work practice alerts, as shown in Figure 4.4 (4 cases for RBC ChE and 18 cases for serum ChE). There was one instance of multiple alerts separated by one or more recovered periodic tests. This observation bears further analysis, as field investigation reports are completed. Research investigations were not conducted for alerts occurring subsequent to the initial alert for the employee.

Exposure removal cases demonstrated ChE activity recovery as follows: 8 out of the 10 cases rebounded to with 20% of baseline within expected time frames, with one of the remaining 2 was not tested again after the depression

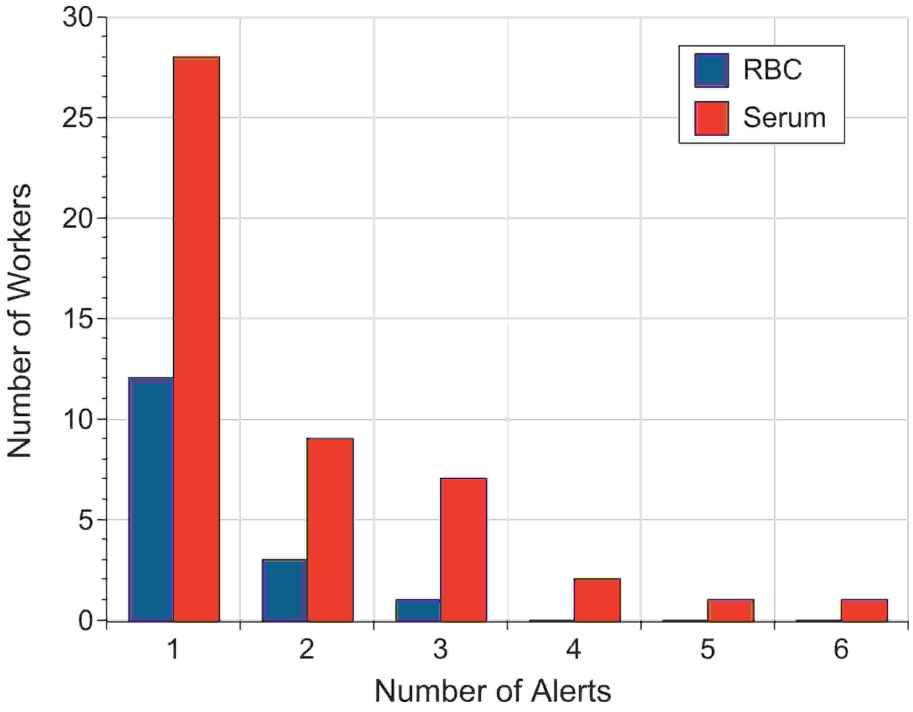


Figure 4.4. Numbers of workers receiving one or more alerts as a result of greater than 20% depression in RBC ChE and serum ChE.

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Nearly all alerts and removals based on excessive depression of both RBC and serum enzyme activity occurred as a result of the first and second periodic test. The timing of these periodic tests corresponds closely to dormant season spraying followed by pome fruit thinning sprays and spraying for the first generation flight of codling moth. During the rest of the growing season, very few alerts or worker removals were issued, although pome fruit orchards typically are sprayed with covered pesticides in June and July. It is worth noting that while the numbers of alerts declined continually throughout the spraying season, the proportion of tests that were at alert levels did not.

Cross tabulation of periodic tests showing >20% RBC and serum enzyme depression revealed five workers who were alerted for both enzyme tests. Both RBC and serum ChE were excessively depressed in these workers. Two workers were alerted twice following excessive depression in both enzymes. Nevertheless, the likelihood of a worker experiencing >20% depression in both tests was very low (0.8% of total workers with a periodic test).

4.8 False Positive and Negative Results

In the 2004 report, this analysis was performed and is found in Appendix 2, pages A.2.4. to A.2.15. The basis for the analysis and background information presented in that report applies equally to the 2005 data, and will not be repeated here. The key result for 2004 is

shown in Table A2.8 and is incorporated in Table 4.6 below. The analysis of 2005 data presented in Table 3.1 includes an estimation of within-person variability (that is, the effect of random variation on ChE activity, including both sample collection or analysis variation and biological variation but excluding the systematic effect of pesticide exposure). Estimates for 2005 are 5.5% CV for RBC ChE and 6.6% CV for serum ChE levels, compared with 9 and 10% seen in 2004 for RBC and serum, respectively. This

		2004 results		**2005 results**	
RBC ChE depression	(notes) ↓	>20% depression	>30% depression	>20% depression	>30% depression
False Positive Rate	a	3.98%	0.25%	0.43%	0.0013%
Number, periodic tests	b	911	911	954	954
Observed positives	c	47	15	21	1
upper bound number of false positives	d	≤ 35.80	≤2.28	≤4.03	≤0.01
% of positives that are false (upper limit)	d	≤76 %	≤15 %	≤19%	**negligible**
number of true positives	d	≥11.2	≥12.7	≥17.0	≥1.0
% of all tests that are true positives (lower limit)	d	≥1.2 %	≥1.4 %	≥1.78%	≥0.10%
Serum ChE depression		>20% depression	>40% depression	>20% depression	>40% depression
False Positive Rate	a	5.73%	0.02%	1.21%	0.00001%
Number, periodic tests	b	911	911	954	954
Observed positives	c	155	29	86	12
upper bound number of false positives	d	≤31.32	≤0.03	≤10.63	≤0.00
% of positives that are false (upper limit)	d	≤20%	≤ 0.09%	≤12%	**negligible**
number of true positives	d	≥123.7	≥29.0	≥75.4	≥12.0
% of all tests that are true positives (lower limit)	d	≥13.60%	≥3.20%	≥7.90%	≥1.26%

NOTES: (A). THIS IS THE FRACTION OF ALL TESTS OF UNEXPOSED HANDLERS THAT ARE EXPECTED (AT 95% CONFIDENCE) TO GIVE A POSITIVE INDICATION OF DEPRESSION. CALCULATED FROM THE %CV AND THE ALERT THRESHOLD. SEE 2004 REPORT, TABLE A2.6. (B) THIS NUMBER INCLUDES ALL PERIOPDIC TESTS BUT EXCLUDES FOLLOW-UP TESTS AFTER EXPOSURE REMOVALAND PRIOR TO RETURN-TO-WORK. (C) THESE NUMBERS OF POSITIVE CASES ARE NOT THE SAME AS NUMBERS OF "WORK PRACTICES "ALERTS "OR "EXPOSURE REMOVAL" ALERTS. FOR EAMPLE, 21 CASES OF DEPRESSION GREATER THAN 20% FROM BASELINE FOR RBC CHE ARE MADE UP OF 20 CASES OF WORK PACTICES ALERTS AND ONE EXPOSURE REMOVAL ALERT. (D) THIS LIMITING VALUE IS BASED ON WORSE-CASE (95 PERCENTILE) NUMBERS OF FALSE POSITIVES AND ASSUMES NO FALSE NEGATIVE CASES.

Table 4.6 – Estimates of maximal numbers of false positive alerts, 2004 and 2005.

improvement in precision was accompanied by changes in frequency of apparent ChE depressions. Comparing the numbers of tests run and the resulting expected numbers of false positives due to random variation with the actual numbers of apparent ChE depression detected gives the results shown in Table 4.6.

In 2005, a number of periodic tests comparable to that from 2004 were run. In 2005, significant reductions in within-person variability (%CV) for RBC and serum ChE resulted in a much lower fraction of tests that were expected to indicate 20% depression or more due to random fluctuations rather than as a result of exposure. For RBC ChE, of the 21 cases indicating >20% depression from baseline, about 4 might be expected to be caused by random error rather than by exposure; the likelihood that the single case of exposure-removal level depression (>30%) was a random effect rather than exposure is very small. This suggests that over 80% of all RBC ChE work practices alerts were triggered by non-random causes, most probably exposure. For serum ChE, the trend is similar, with over 88% of all work practices alerts and essentially 100% of all exposure removal alerts being caused by non-random effects. This is a substantial improvement over the 2004 experience.

The apparent frequency of RBC depression at 20% after adjustment for possible false positives as 95% confidence levels remains at least 1-2%; for serum it is around 10% (≥14% in 2004, ≥8% in 2005). (The frequency of true positives is this number plus the unknown frequency of false negative results). This indicates that there remains in this program a population of workers to protect, for whom monitoring will serve as a useful early warning.

The problem of estimating a rate of false negative results was detailed in the 2004 report, in Appendix 2, and remains unchanged by the 2005 data. Given that the upper limit for numbers of false negatives is a large number (nearly all tests run) and that there is no way to estimate how much true exposure is occurring other than by using the test results, any estimate of fraction of negative tests that are false is too uncertain to be useful. This poses an additional difficulty in attempting to determine the true rates of exposures (leading to >20% ChE depression) in the population of pesticide handlers, and it must be emphasized that estimates based on apparent positives or apparent positives corrected for expected false positives (as is shown in Table 4.7) will underestimate the prevalence of ChE depression by an unknown amount.

4.9 Adding a Second Baseline Sample: Effect on False Alerts

Coefficient of variation	False Positive Alerts, 1 baseline	False Positive Alerts, 2 baselines
5 %CV	0.4	0.05
6 %CV	2.1	0.6
7 %CV	6.1	2.3
8 %CV	12	5.7

9 %CV	20	11
10 %CV	29	17

Table 4.7 – Expected upper-bound false positive tests per 500 workers tested

Table 4.7 above indicates the number of false positive alerts expected per 500 workers tested for test data with a known precision (%CV), if one or two baseline samples are tested. The false positive rate is calculated for the >20% depression alert level. In 2004, the precision values estimated were 9%CV for RBC ChE and 10%CV for serum ChE. In 2005, the corresponding values were 6% CV for RBC ChE and 7%CV for serum ChE.

Given measurement variability typical of the monitoring data, adding a second baseline measurement reduces the error rate to about one-third of the error rate from a single baseline. Applying these error rates to the 2005 monitoring data gives the following predicted number of false positive results:

	Apparent alerts, 2005 (>20% depression)	FP cases, 1 baseline	FP cases, 2 baselines	Difference (cases avoided)
6 %CV (RBC rate)	20	4.03	1.1	3
7 %CV (serum rate)	74	11.5	4.4	7

Table 4.8 – Marginal benefit of a second baselines estimated for 2005.

The effect of a second baseline on false positive exposure removal alerts is inconsequential since no cases of false positive alerts are predicted, even with a single baseline (refer to Table 4.6). Out of about 94 cases of work practice alerts in 2005, adding a second baseline samples (that is, collection and assay of about 2300 blood samples) would potentially avoid up to 10 instances of a false "work practices" alert. This does not appear to the Scientific Advisory Committee to be a compelling case for adding a second baseline test to the Rule requirements.

4.10 Workplace Characteristics and Alerts

The time trend in alerts is consistent with the hypothesis that the greatest proportion of ChE depressions exceeding the benchmark of 20% from baseline occurred primarily during dormant season spraying of tree fruits. Secondarily, alerts tended to be coincident with timing of fruit thinning sprays and the use of post bloom cover sprays for the control of the first generation of codling moths. During dormant season spraying, the organophosphate insecticide chlorpyrifos is used. The observation that many of the alerts were due to depression of serum ChE is consistent with the use of chlorpyrifos because it is recognized as being a more potent inhibitor of this enzyme than of RBC ChE. Carbaryl, typically thought of as a methyl carbamate insecticide, has plant growth regulator properties that cause abortion of small fruit. The pome fruit industry relies heavily on its use in late April and early May for thinning. Carbaryl may be applied up to two times, about 10 days apart. Finally, by mid May many orchards have laid down one cover spray for controlling codling moths. Guthion (azinphos-methyl) remains the most used of the available insecticides. The number of alerts dropped precipitously during the rest of the growing season. This drop reflects the infrequency of later cover sprays for codling moth control. The comparatively small number of alerts after May and

the differences in numbers between 2004 and 2005 may also reflect a growing tendency in the fruit tree industry to use reduced risk insecticides that are not covered by the monitoring regulations.

4.11 Relationship Between Hours Worked and Resulting Enzyme Depression Levels

Reporting of hours was improved during 2005 in comparison to 2004. The compliance rate was estimated to be 92% based on 562 handlers' reports of zero or more hours worked in the 30 days prior to the first periodic test and 611 total handlers submitting a sample.

Modeling of the effect of reported hours of pesticide handling on ChE depression showed no relationship for RBC ChE. Reported hours did have a statistically significant predictive value for serum ChE depression, amounting to an average depression of 1.6% for a handler with 30 hours pesticide use. This effect is smaller than the amount of serum ChE depression actually seen (an average of 4.5% depression from baseline to first periodic test, combined with a slightly larger amount of random change (either direction) in ChE activity). Thus, while there is a demonstrated relationship between hours of pesticide handling and ChE depression, hours of handling is not a strong predictor of the degree of ChE depression for individuals. This suggests that hours may be a qualitative surrogate for other exposure factors (such as work practices, the specific pesticides being used, etc) occurring in the workplace. Further investigation of what the most robust predictors of ChE depression are is an ongoing need.

More analysis and follow up discussion among SAC members will be required to fully understand the relationship between hours worked and trends in enzyme activity, and will be in the final report for 2004-2005 to be completed in August 2006.

4.12 Summary

Comparable numbers of samples were tested in 2005 compared with 2004 and the overall characteristics of the pesticide handler population remained similar. The ~1150 pesticide handlers monitored in both 2004 and 2005 had similar baseline ChE levels between years. There was a small but statistically significant decrease in serum ChE activity in 2005, but the 1% magnitude would not represent an important determinant of overall activity levels. Red blood cell ChE showed a significant but larger effect (6% decrease in 2005) that may reflect improvements in RBC ChE analysis in 2005.

Both serum and RBC ChE showed statistically significant decreases in overall activity level between baseline and first periodic test: about 2% average decline for RBC ChE and approximately 4.5% average decline for serum ChE. ChE depressions were distributed among pesticide handlers throughout the 2005 monitoring season as follows. For RBC ChE, 81.1 % of pesticide handlers showed increases or decreases of less than 10% from baseline activity (some portion of which might be due to factors other than pesticide handling), 10.2% showed >10% to 20% depression, 2.2 % showed >20% to 30% (and

had one or more "work practices alerts"), and 0.2% (one handler) had an instance of RBC ChE depression >30% with a resulting exposure removal alert. For serum ChE, 66.5% of pesticide handlers showed increases or decreases of less than 10% from baseline activity, 22.0 % showed >10% to 20% depression, 7.8 % showed >20% to 40% (and had one or more "work practices alerts"), and 1.3 % (12 handlers) had serum ChE depression >40% with a resulting exposure removal alert. There were several examples of pesticide handlers with multiple alerts: 59 handlers had an alert from one or both ChE tests, and multiple alerts accounted for 107 tests showing greater than 20% ChE depression from baseline.

The majority of all alerts occurred early in the monitoring season, by the end of June. All of the alerts were associated with tree blast spraying operations (but details of pesticide, method of application, and formulation used are only available from consultations following an alert).

Statistical analysis comparing the within-handler variability (from causes other than pesticide exposures) with the number of tests run and the number of apparent cases of >20% ChE depression indicates that in 2005, the >20% depression alert trigger was highly reliable: for RBC ChE, at least 81% of alerts were likely to be correct, and for serum ChE, the 20% alert level was at least 88% reliable. At the exposure removal level (>30% depression for RBC ChE and >40% depression for serum ChE), both tests were essentially 100% reliable. These results are significantly improved over those from 2004, and reflect improved analysis performance.

The frequency of true positive alerts (>20% depression) was at least 1-2% of all periodic tests for RBC and at least 8% for serum ChE (down from 14% in 2004). The discrepancy between frequency of positives from RBC versus from serum tests may arise from analytical differences in the sensitivity of the two tests and/or may reflect differential effects of the pesticides used on the two enzyme systems tested. For whatever reason, serum ChE appears to be the more useful marker at this point.

Further improvement of the reliability of the tests by addition of a second baseline sample (with not other improvements in analytical quality assumed) would be expected to decrease the number of false positives to about 1/3 of the rate estimated for 2005. This would potentially have avoided 3 instances of false positive tests for RBC ChE at the "work practices" alert level and about 7 instances of a serum ChE false positive work practices alert in 2005. No instances of false positive "exposure removal" alerts were indicated for 2005, so additional baseline samples would not be expected to have had an effect on this outcome.

A preliminary regression analysis suggests no trend between decreased RBC ChE activity levels and increasing hours worked. However, the analysis does indicate a statistically significant trend between increasing hours worked and increasing depression serum ChE activity. The amount of serum ChE change that could be predicted based solely on pesticide handling hours is small compared to the serum ChE changes actually seen.

More analysis and follow up discussion among SAC members will be required to fully understand the relationship between hours worked and trends in enzyme activity.

Chapter 5: Assessment of Program in 2005

This section provides information related to the evaluation and implementation of the ChE monitoring program. It focuses on four aspects of the ChE monitoring program. They are:

- Assessing employer enrollment of pesticide handlers in the ChE monitoring program;
- The timeliness of the ChE monitoring system in processing samples and reporting results;
- Reports of symptomatic organophosphate and carbamate related illness from the Pesticide Incident Review and Tracking (PIRT) Panel; and
- WISHA research investigation visits to employers as part of the ChE monitoring program.

5.1. Employer Enrollment of Pesticide Handlers into the Cholinesterase Monitoring Program.

In 2005, the ChE Monitoring Rule required employers to enroll handlers in the ChE medical monitoring program if the hours of organophosphate (OP) and N-methyl-carbamate handling activities were expected to meet or exceed 30 hours during any consecutive thirty-day period. Handlers were referred to a health care provider for initial medical evaluation and consideration for inclusion in the ChE testing program. The rule required baseline ChE testing to be completed after at least a 30-day period during which the employee had not handled OP and N-methyl-carbamate pesticides. This process was required for all covered handlers even if they had participated in the 2004 medical monitoring program. The experience of handlers in the year 2005 ChE monitoring program, grouped by number of participants per employer, is presented in Table 5.1.a. For comparison, summary results from the 2004 season are also included.

Table 5.1.a: Baseline periodic testing for Cholinesterase monitoring program participants by # of participants per employer, Washington State 2005.

Number of Participants per Employer	Number of Employers	Total Base-lines	Number of Participants with at Least One Periodic Test	Percent of Participants with at Least One Periodic Test	Number of Participants with at Least One Depression	Percent of Participants with at Least One Depression
≥ 50	7	578	146	25%	9	6%
11 - 49	44	883	276	31%	33*	12%
1 - 10	261	802	189	24%	17	9%
Total (2005)	312	2263	611	27%	59	10%
Total (2004)	370	2655	580	22%	119	21%

* Eight of these 33 participants worked for a single employer. This is the largest number of employees with significant ChE depression from a single employer.

In 2005, 312 employers and 2263 workers participated in the program, representing decreases of 16% and 15%, respectively, compared to 2004. The largest number of participants from one employer was 144; the median was 3 and the mean was 7.3 workers per employer. While the number of baseline tests dropped between 2004 and 2005, both the number and the percent of participants who had at least one periodic test increased. In 2005, about 10% of participants had at least one depression requiring either a workplace investigation or exposure removal. This is about half of the 21% of participants who in 2004 had one depression at best.

Employer compliance with the rule was not systematically assessed. Spot checks of 17 growers (all in Region 5, with SIC codes of 175. 723. 5148, and 139) indicated that 14 of the 17 had employees enrolled in the 2004 ChE monitoring program, and of the remaining 3, either no covered pesticides were used or minimum handling hour requirements were not met. One employer, all of whose employees declined participation in the monitoring program, was cited for noncompliance with recordkeeping requirements (hours of use of class I and II pesticides).

Selected individual employer level data from the 24 employers who enrolled at least 25 handlers for baseline testing in 2004 and 2005 are presented in Table 5.1.b. Employers are ranked by the combined enrollment in ChE monitoring for 2004 and 2005.

Table 5.1.b – Comparison of enrollment and periodic testing for employers who had enrolled ≥25 handlers in the 2004 or 2005 testing program.

Employer	# handlers with baselines in 2004	# handlers with at least 1 periodic test in 2004	# handlers with baselines in 2005	# handlers with at least 1 periodic test in 2005
A	118	35	81	49
B	69	0	81	0
C	55	36	59	12
D	30	18	32	18
E	36	2	21	10
F	28	8	23	11
G	31	2	19	0
H	15	2	31	2
I	32	8	13	0
J	39	2	4	3
K	17	6	25	10
L	25	2	15	9

Without additional information, it is difficult to interpret these data both at the individual employer level and in aggregate. For example, on the one hand, given that the threshold for referral was decreased from 50 hours of handling covered pesticides in a consecutive 30-day period in 2004 to 30 hours in 2005, the SAC had expected the number of

employers and workers with baselines to increase. On the other hand, the SAC encouraged L&I to work with growers so that they did not refer for baseline testing workers who ultimately would not meet the criteria for periodic testing. Referring fewer workers who would not ultimately meet criteria for periodic testing might reduce both the number of employers (i.e. growers who in 2004 referred workers for baselines and had no workers with periodic tests) and the number of baseline tests. The data showing an increase in the number and percent of participating employees with periodic tests suggest that in 2005, employers were in aggregate better able to identify who needed to be referred into the program.

Other factors that might have contributed to a decrease in participating employers include:

- Changes in pesticide use patterns from 2004 to 2005;
- Rotating workers such that they no longer met the referral criteria;
- Employer non-compliance; or
- Worker refusal to participate.

Likewise, there are several factors that could be contributing to the substantial decrease in the percent of workers with depressions requiring a workplace evaluation or an exposure removal. The improvements noted in laboratory procedures and data precision may be one contributing factor. Improved pesticide handling practices resulting in less overexposure would likewise result in a decrease in the percent of workers with depressed ChE levels. Organizational changes made by growers to reduce handling hours per individual, or decisions by handlers to cease handling pesticides could plausibly contribute. A decrease in the percent of workers with depressed ChE might also be seen if workers or growers with unsafe handling practices disproportionately refused participation in ChE monitoring compared to 2004.

Table 5.1.c: Declination rates at the five clinics providing the most baseline ChE blood samples.

Provider #	# Baselines submitted	# Workers declining	% Declining
36	559	65	10.4%
42	117	1	0.8%
37	73	10	12.0%
14	106	14	11.7%
57	701	120	14.6%
41	162	22	12.0%
Total	1718	232	11.9%

In an attempt to assess the proportion of handlers offered participation in the program who declined testing from the health care provider, L&I surveyed the five health care clinics performing the most baseline ChE tests. Each clinic was asked how many handlers were referred to the clinic and how many declined participation. All clinics had a less than 15% declination rate (Table 5.1.c). There are no comparable data for 2004. The 2003 Cholinesterase Monitoring Small Business Economic Impact Statement estimated that the

declination rate would be approximately 15% (available at http://www.lni.wa.gov/wisha/Rules/agriculture/PDFs/SBEIS-Cholinesterase.pdf).

5.2. Timeliness of the cholinesterase monitoring system in processing samples and reporting results.

Timeliness of laboratory receiving and processing samples and reporting results is essential to preventing subsequent exposure and mitigating the potential for pesticide poisoning. The laboratory SOP specified time periods for the handling and processing of lab specimens. L&I established timelines for reporting significant ChE depressions. Table 5-2 provides the information on the optimum timeliness of the reporting and the actual results for the 2004 and 2005 seasons.

In 2005, all performance goals were met or exceeded, except for the number of days between notification of the research investigator and the site visit for ChE depressions to the exposure removal level. This latter activity showed marked improvement over the 2004 performance, as did other activities that did not meet goals in 2004. When measured in business days the average time period between research investigator notification and site visit for work practice evaluations was 9.4 days and for exposure removal investigations, 6.8 days. For work practice evaluation investigations 23/36 occurred within the performance goal of 14 days, whereas 2/6 workplace removal investigations occurred within the performance goals.

The improved efficiency of the ChE monitoring system was due to the experience gained from the 2004 season. L&I and DOH allocated resources to improve the timeliness of several components of the system (e.g. a dedicated WISHA research investigator and the preparedness of the PHL for processing a large number of baseline and periodic samples). In 2005, L&I verified with the provider that notification of the employer occurred in all cases of exposure removal. In all cases, notification occurred on the same day and usually within a few hours. L&I did not immediately confirm notification for ChE depressions to the work evaluation level. Improved understanding of the ChE monitoring program research investigations by growers may also have contributed to more timely research investigations of worksites. Grower representatives also commented that the assigning of a dedicated and specifically trained field investigator/consultant for this purpose also aided in achieving timely consultations.

Table 5.2 Time Periods in Calendar Days for Selected Steps in Cholinesterase Monitoring System

Time Period Measured	Performance Goal (Days)	2004 Average Time (Days)	2005Average Time (Days)
Baseline Testing			
Blood draw and receipt by PHL	1	1	1
Receipt by PHL to test	1	25	1
Periodic Testing			
Blood draw and receipt by PHL	1	1	1
Receipt by PHL to test	1	1	1
Mailing test report to provider and transferring information to CMDS	3	4	2
Periodic Tests Requiring Work Practice Evaluation			
From test date to L&I informs health care provider	6	6	5
Research investigator (RI) notified to site visit	(14)[1]	35	13
RI notification to employer contact	---	---	6.6
Employer contact to site visit	---	---	6.6
Periodic Tests Requiring Exposure Removal			
From test date to L&I informs health care provider	6	4	4
Research investigator notified to site visit	5	35	9.5
RI notification to employer contact	---	---	5.2
Employer contact to site visit	---	---	4.3

[1] This performance benchmark is not stated in the rule, but was used by L&I program managers and is consistent with the 3 weeks prescribed for the interval between notification to the region of an alert and the scheduling of a field investigation.

5.3. Reports of organophosphate and carbamate related illness from the Washington Department of Health Pesticide-Illness Monitoring System.

The Washington State Department of Health (DOH) Pesticide Program conducts surveillance for pesticide related illness and injury. Findings are published annually in the Pesticide Incident Reporting and Tracking (PIRT) System (http://www.doh.wa.gov/ehp/ts/PIRT.HTM).

As part of the information to augment this SAC report regarding the ChE monitoring system, we requested information from the DOH pesticide program regarding the number of pesticide illness cases resulting from exposure to ChE inhibiting pesticides in occupational agriculture (Table 5.3).

In 2004, there were six cases of illness or injury involving workers enrolled in the monitoring program that were considered, after DOH investigation, to be definitely, probably or possibly related to handling ChE inhibitors. These are described below along with five cases in workers who were not enrolled in the monitoring program.

Table 5.3. Illness Type* for Pesticide Handlers** by Cholinesterase Inhibiting Pesticides, 2000 - 2004

Pesticide	2000		2001		2002		2003		2004		Totals	
	Sys	Top	Sys	Top	Sys	Top	Sys	Top	Sys	Top	Sys	Top
Azinphos methyl	1	1					1		2		4	1
Chlorpyrifos	2								2		4	
Dimethoate			1							1	1	1
Disulfoton									1		1	
Ethoprop							1				1	
Combinations of ChE inhibitors with other products	7	2	4	4	1	3	3	1	3	2	18	12
Totals	**10**	**3**	**5**	**4**	**1**	**3**	**5**	**1**	**8**	**3**	**29**	**14**

* *Type of illness/injury: Sys = Systemic: Any health effects not limited to the skin and/or eye. Top = Topical: health effects involving only the eyes and/or skin.*

** *Agricultural workers who handle ChE inhibitors via mixing, loading, applying, or repairing equipment.*

We reviewed an initial draft of the 2005 PIRT report, which summarizes the 2004 data. There were eight cases of definite/probable/possible systemic and respiratory illnesses due to ChE inhibiting pesticides reported to PIRT in 2004. The number of reports for systemic illness from ChE inhibiting pesticides in 2004 is within the range of that from previous years. Due to annual fluctuation in the number of reports and the relatively small number of reports each year, we cannot conduct a statistically meaningful trend analysis. Three additional cases of ChE inhibiting pesticides health effects to the skin and eyes were reported.

From the draft PIRT report:

All but one of the eleven PIRT cases sought health care in a hospital emergency room or clinic. This person received health care from his regular occupational health physician. Eight of the eleven cases occurred in tree fruit operations, mostly apples. The other three occurred at an onion farm, an unspecified farm, and an ornamental nursery. No cases involved aerial application. Most cases involved using (5) or cleaning/fixing (2) orchard ground sprayers.

There were four cases of applicators driving orchard airblast sprayers who stated that they wore the proper PPE, wore fit-tested respirators and who still had symptoms and/or significant cholinesterase inhibition. These workers told DOH in interviews that they sometimes still smell the chemicals through the cartridges and feel mist on their face when they turn the corner at the end of a row. One of these workers had 80 percent depression on his plasma cholinesterase activity[1] A fifth orchard airblast sprayer was exposed when his positive pressure helmet caught on wires in the orchard and flipped off his head.

Two men were exposed while cleaning sprayer nozzles or fixing a sprayer. Cleaning and repairing contaminated equipment is considered "handling" and full pesticide handler's PPE is required. In both cases the mechanic only wore rubber gloves. One of these mechanics experienced systemic symptoms and at least a 23 percent depression in plasma ChE.[2] The other developed respiratory symptoms and contact dermatitis where pesticides from the sprayer hit his forearms.

There were two handlers who had exposures while transporting pesticide to the loading site or putting away a cleaned sprayer. Both were in the handling area but did not have on PPE because they had not yet started or had just finished their direct handling duties. Both were exposed to spray from other handlers in the area. PPE should be worn at mixing and load sites and in areas where sprayers are being washed.

Six of the eleven cases participated in the ChE monitoring program and all were in the tree fruit industry. Two had only baseline testing and four had periodic testing. The four handlers with periodic tests were applicators using air blast sprayers. Two handlers had significant serum ChE depressions (80% and 57%) and two had no depressions relative to their baselines in ChE testing done 10 days post incident. The DOH Pesticide Program received the report of the handler with an 80% ChE depression through a workers' compensation claim[3]. The depressed ChE level led to further evaluation of the handler's work activities and his health status. No single acute exposure was traced to his depressed ChE level. The fourth handler, an applicator doing air blast spraying, had an acute

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[1] This handler was asymptomatic and was referred to PIRT based on his prior ChE monitoring data

2. The mechanic was not enrolled in the cholinesterase monitoring system. The determination of the 23% plasma cholinesterase depression was through sequential plasma cholinesterase testing at a commercial laboratory. A plasma ChE level at the time of systemic symptoms was compared a plasma ChE activity several weeks after recovery from his systemic symptoms. There was a 23% improvement in plasma ChE activity on follow-up testing.

3. In the report Cholinesterase Monitoring of Pesticide Handlers in Agriculture: 2004, this committee reported that there were no accepted industrial insurance claims related to the cholinesterase-monitoring program. This statement remains correct as of the present time.

exposure resulting in a topical illness thirty days after his baseline testing. A subsequent periodic test 30 days following the acute exposure revealed the 57% ChE depression.

Five cases of illness related to ChE inhibiting pesticides were not enrolled in the in the ChE monitoring system. Of the five cases, two had sufficient exposure information to exclude them from the requirement for enrollment in the ChE Monitoring Rule. For the three remaining cases, there was insufficient exposure information to determine whether they should be included in the ChE monitoring system.

Several conclusions can be made from looking at the DOH pesticide program data:

1. Given the annual fluctuation and the relatively few cases of symptomatic ChE inhibiting pesticide poisonings reported to the DOH pesticide program each year, it is too early to use the data to assess the effectiveness of the ChE monitoring rule in reducing pesticide poisoning.

2. A portion of the DOH pesticide program cases result from acute exposures to covered pesticides. These events typically do not trigger ChE testing within the ChE monitoring program suggesting a gap in coverage of the ChE monitoring rule.

3. Some DOH pesticide program cases cannot identify a specific exposure incident e.g. regarding applicators driving airblast sprayers '*still smell the chemicals through the cartridges and feel mist on their face when they turn the corner at the end of a row'*. The occurrence of illness in workers without specifically recognized exposures supports the requirement for periodic ChE testing.

4. The present ChE monitoring program triggers periodic testing based on hours handling and not as a result of an unexpected acute exposure. Health care providers are not allowed to send ChE measurement to the PHL following an acute symptomatic exposure. Since blood tests from different laboratories are often not comparable, doctors lose the ability to compare a test result at the time of symptoms with the worker's pre-established baseline from the ChE monitoring program. If a worker has an established baseline within the ChE monitoring program, the SAC recommends sample submission to the PHL following an acute exposure, which leads to symptomatic illness.

5.4 WISHA Research Investigation Visits to Employers as Part of the Cholinesterase Monitoring Program.

As part of the rule evaluation process in 2005, L&I offered research investigations under RCW 49.17.210. A dedicated, bilingual research investigator was assigned to coordinate the program and conduct investigations.

The investigation protocols and data gathering tools are contained in WISHA Regional Directive 33.27 Cholinesterase Depression. In summary, to facilitate the collection of

information and to assist employers with their employee safety and health efforts, WISHA offered research investigations to employers in response to employee ChE depression >20% from baseline.

Generally, the research investigation evaluates an employer's performance under the pesticide worker protection standard and ChE monitoring rules. More specifically, investigations sought to identify factors that could have contributed to the employee's overexposure. This included an evaluation of the equipment (including PPE) and facilities provided by the employer, and the employee's knowledge and ability regarding use of the facilities and equipment. Each employee with a depression was contacted and interviewed whenever possible. Possible non-occupational factors were not targeted in these investigations; only specific questions asked were in regards to personal use of ChE inhibitors, potential drift exposure, and residence on farm site. One general "other" question that might identify possible non-occupational ChE depression was asked of the employer and employee.

Forty-two research investigations were conducted from March 31 to August 19, 2005. Due to the staggering of ChE depressions some employers who had multiple employees with significant depression were visited more than once. At the time of writing, only one of the 28 employers who had an employee with a significant ChE depression had not yet scheduled a site visit after being contacted by the L&I research investigator.

As in 2004, all significant ChE depressions occurred in L&I Region 5, which is composed of Okanogan, Chelan, Douglas, Kittitas, Grant, Yakima, Adams, Franklin, Benton, Walla Walla, and Columbia counties. Overall, 28 (9%) employers had 59 workers with at least one significant depression (i.e. at least one depression greater than 20%).

- 12 employers each had one employee with a depression to the work practices investigation level.
- 11 employers had two workers with significant depressions, 9 with two workers with depressions to the investigation level and two with one worker with a depression to the investigation level and one worker requiring exposure removal.
- One employer had three workers with depressions to the work practices level.
- One employer had two workers with depressions to the work practices level and one worker to the exposure removal level
- Three employers had five or more workers with significant depressions overall and at least one worker requiring exposure removal:
    - One had four workers with depressions to the work practices investigation level and one worker requiring exposure removal.
    - One had six workers with depressions to the work practices investigation level and two requiring exposure removal.
    - One had eight workers with depressions to the work practices investigation level and four requiring exposure removal.

Thus, five employers (those with three or more workers with depressed levels) were responsible for about 44% of the significant depressions overall and 80% of the exposure removals.

L&I was able to conduct research investigations on all but one of the cases of ChE depression greater than 20% from baseline (27 employers had research investigations). As noted in section 5.2, the response time for conducting research investigations was much improved over 2005. In 2004 there were several reasons for the delay in conducting investigations including 1) lack of clarity about the process, 2) poor communication between the health care provider and employer, 3) unresolved employee confidentiality issues. In 2005, employers were much more willing to work with L&I to schedule investigations. WISHA Policy and Technical Services (P&TS) was able to provide the research investigator with the identity of the employee, level of ChE depression, and more accurate employer contact information.

P&TS confirmed that the health care provider had informed the employer of all ChE depressions to the exposure removal level and scheduled employee follow-up testing prior to notifying the research investigator. All research investigations of employees with ChE depressions to the exposure removal level confirmed that the employee was removed from handling covered pesticides immediately upon health care provider notification. All of these employees were shifted to other duties while being monitored for ChE recovery. One employee shifted to other duties was not being paid the handler rate. This was immediately corrected once the research investigator clarified the employer's responsibility to provide medical removal protection benefits as defined in WAC 296-307-14830.

There were 42 investigations, some of which covered multiple significant depressions. Eighteen of the investigations were to orchards with between 100 and 500 acres. Apples were the only crop grown at nine of these orchards, with the remaining orchards growing a combination of apples and other fruits including cherries (8), pears (6), grapes (2), and peaches (1). Ten investigations were to orchards with between 540 and 1000 acres. All of these orchards grew apples and cherries, with eight also growing other fruits including pears (6), grapes (4), peaches (2), and plums (1). The 12 orchards were between 1100 and 5000 acres. All of these orchards grew apples and at least one other type of fruit including cherries (8), pears (10), peaches (4), nectarines (2), pluots (2), apricots (2), grapes (1), and/or blueberries (1). Information on acreage was unavailable for one investigation where apples were the only crop. The investigations did not determine which crop(s) the worker was involved with when the ChE depression occurred. That all of the investigations were for workers involved with fruit crops is similar to the experience in 2004, where all but two investigations involved orchards, and two involved potatoes. The pattern of significant depressions in relation to crop type is difficult to interpret. There is no information from these investigations about the types of crops grown by employers who did not have employees with significant depressions, employers who should have participated in the program but did not, or employee declination. The number of handlers at each of the orchards ranged from 2 to 50, with missing information for 12 of the orchards.

One of the goals of the research investigation process was to assist employers with their employee safety and health efforts. To achieve this goal the research investigation process included an evaluation of the employers' performance under the pesticide worker protection standard, WAC 296-307-107 through 296-307-148, and other related sections under chapter 296-307, Safety Standards for Agriculture. At the close of each investigation the investigator provided the employer with a report of the findings. The report included information about suspected routes of exposure and a listing of any rule violations identified, other findings, recommendations, and an explanation of the employers' responsibilities to correct any violations. This included the requirement to correct serious violations within 30 days and to notify the investigator of the corrective actions taken. The investigator had the option to approve a shorter or longer abatement period based on the circumstances of a particular investigation.

Rule violations and potential routes of overexposure found during research investigations are summarized as follows:

Respiratory protection – There were 31 violations of WAC 296-307 Part Y. The majority of violations involved the lack of an appropriate respirator cartridge or change out schedule. Other common violations included failure to provide medical evaluations and appropriate fit testing. The following are examples of potential causes of overexposure identified by the research investigator:

- The use of a half-face respirator leaving the skin above and around the respirator opened to contamination
- Use of damaged or worn respirators
- Use of a respirator with an uncomfortable fit
- Not using cartridge prefilter specified by product label, (using N filter when using oil mixture)
- Allowing facial hair on tight-fitting respirator users
- Failure to decontaminate respirators after use

Personal protective equipment - There were 17 violations of WAC 296-307-13045. The majority of violations involved not wearing appropriate chemical resistant headgear when required by the pesticide product label. Other common violations related to failure to clean and decontaminate personal protective equipment. The following are examples of potential causes of overexposure identified by the research investigator:

- Not decontaminating personal protective equipment after each use, including meal and bathroom breaks
- Wearing cotton baseball style caps under a hood. The brim of the cap extends beyond the hood and becomes contaminated while spraying
- Wearing cotton gloves under chemical resistant gloves
- Not using personal protective equipment specified on the pesticide product label
- Cleaning spray nozzles without gloves

Decontamination - There were 12 violations of WAC 296-307-13050. The majority of violations involved failure to provide emergency eye flushing. Other violations related to

failure to provide appropriate plumbed emergency wash stations in mixing and loading areas, and not providing a clean change of clothing for use in emergencies. The following are examples of potential causes of overexposure identified by the research investigator:

- Not washing face and hands thoroughly and immediately after application and when going on breaks or for lunch
- Not following decontamination procedures

Pesticide handler training – There were 6 violations of WAC 296-307-13925. These violations generally cited a failure to provide specific information about pesticides and routes of exposure.

Pesticide safety information - There were 3 violations of WAC 296-307-13040. These violations generally cited failure to post information on pesticide applications and restricted-entry intervals.

First aid – There was 1 violation of WAC 297-307-03930. The employer did not assure that emergency washing stations were functional.

Safe operation of equipment – There was 1 violation of WAC 296-307-13035. The employer did not ensure that equipment was appropriately decontaminated prior to maintenance.

Cholinesterase monitoring - There was 1 violation of WAC 296-148. The employer did not maintain the pesticide handler pay rate of an employee who had been removed from exposure due to a significantly decreases ChE level.

Despite the rule violations employers generally had active pesticide worker protection programs in place. Only one violation of the ChE monitoring rule was found. Additional possible routes of overexposure included:

- Use of cell phone while handling pesticides
- Smoking while handling pesticides
- Showering at home after applying pesticides
- Burning empty pesticide containers

Potential causes for overexposure identified during the 2005 research investigations generally mimic those found in 2004. The results of L&I consultation activities contained in the *2004 Cholinesterase Monitoring of Pesticide Handlers in Agriculture Report to the Legislature* (http://www.lni.wa.gov/Safety/Topics/AtoZ/Cholinesterase/files/final.pdf) may be referred to for observations and recommendations regarding these potential exposure scenarios. It should be noted however, that the research investigation program considers only workplaces where alerts have occurred and was not developed with the intent to evaluate by way of comparison with workplaces where participation in the system occurred, but no depressions developed. This necessarily limits the ability to draw general conclusions regarding industry-wide causal factors.

For workers with medical removal or worker alert levels, covered pesticides handled during 2005 were Lorsban, Guthion, Carzol, & Imidan (refer to chapter 6 for further discussion of pesticide exposure). Air blast spraying with Lorsban appears to be a common activity among workers with significant ChE depressions. As noted in 2004, approximately 50% of employers investigated are using a Lorsban product that does not include a label requirement for respiratory protection.

Chapter 6: Issues and Recommendations

This section restates the major recommendations for the ChE monitoring program, and identifies longer term issues for consideration. In general, good to excellent progress in all phases of the program between its launch in 2004 and the second monitoring year was noted. Continuation of those efforts to improve the program, including laboratory aspects, external quality control, or improving communication with and educational outreach to health care providers and growers is an over-arching recommendation.

6.1 Summary of recommendations

Recommendations from the earlier chapters in this report were:

- Matching of periodic and baseline test by worker. This time-consuming process could be improved by the issuance of unique identifiers to participating workers. Such a modification could be evaluated in terms of its overall benefit to system accuracy and efficiency.
- Select and implement procedures to assure timely communication of ChE test results to the pesticide handler. As a medical standard of care, notification of a patient's laboratory test results is incumbent upon the health care provider. Other suggestions to improve notification of workers of their ChE results include requiring the employer to inform the worker or to contract with a health care provider who will agree to inform the handler of his or her test results
- The Scientific Advisory Committee suggests that L&I have extensive interaction with both the SAC and the Cholinesterase Monitoring Stakeholder Group in managing program transitions (such as contracting with a private laboratory for ChE testing, discontinuation of L&I subsidizing ChE laboratory testing and program maintenance expenses, and potential loss of the assistance provided by state agencies to data flow for the ChE monitoring system).
- The PHL should develop and use a formal QC checklist as part of data validation.
- The PHL is encouraged to maintain the procedural and organizational improvements adopted between 2004 and 2005
- Determining the longer-term role of the PHL in this monitoring program is highly desirable if the lab is to make strategic plans to develop this assay further.
- Inter-lab exchanges and development of a robust control material for RCB ChE is still needed
- Modification of the sample submission form and/or improved provider training to avoid confusion over pesticide handling prior to collection of baseline samples is recommended.
- The Scientific Advisory Committee does not recommend adding a second baseline test to the Rule requirements, based on apparent benefits estimated from 2005 data.

- Employee declinations should continue to be tracked, as an indicator of educational outreach and overall coverage of the target population under this rule.
- Continue to improve timeliness in alert follow-up, whether this takes the form of a field research investigation (not planned as a routine occurrence, for 2006), or a compliance action.
- The SAC and L&I should continue to examine the results of field investigations as these are completed, and consider exposure/depression patterns in the workplace. Of particular interest are handlers with repeated or continual depressions at the alert level for several monitoring cycles.
- If a worker has an established baseline within the ChE monitoring program, hospital emergency rooms and health care providers are permitted to submit samples to the PHL following an acute exposure that leads to symptomatic illness. However, this is not widely advertised and may represent a lost opportunity to get medical benefit from prior baseline testing. More outreach to hospitals and health care providers on this point is recommended.

6.2 Issues

Beyond procedural improvements to program aspects already underway, there are some issues that ought to be considered for planning purposes in preparation for 2006 and later.

1. The "Evaluation Plan", which we recommended in 2004 be extended to address all aspects of the ChE monitoring effort, still has some gaps. Examples include lack of information on: 1) percent of covered growers participating in the program;. 2) Percent of handler declining participation; 3) types of crops grown by participants with no workers with overexposure.

Expectations of providers under the rule, such as discussions with a handler following a ChE depression alert to determine whether there were potential confounding factors that might apply, also do not have an evaluation component at present.

2. Planned changes to the monitoring program: The role of the CMDS as a central repository of monitoring program data has been key to timely notification and follow-up of depressions and for assuring correct results. Future program changes will need to provide for continuation of these functions. The most straightforward way to accomplish this would be to obtain continued participation from WDOH to provide this service, if that is compatible with other program changes.

3. Notifications to Handlers: since the start of the monitoring program, L&I has been the main notifier of providers and employers when alerts occur. In 2006 L&I is planning on continuing provider telephone notification of alerts. This will presumably cease with the transition to a commercial lab in 2007. There are no data or plans in place to assess provider performance in the timely recognition of depressions and notification to employers and L&I. Also, we still do not know how long it would take a provider to

figure out that a worker has a depression and then to notify the employer or employee about the depression, since L&I has been notifying the provider. If L&I is planning to end or change its role in this notification, 2006 would be an opportune time to try and figure out what happens in the field in the absence of L&I calling providers, since CMDS will still be in operation.

4. Transfer of lab analysis to a new organization: the Rule originally intended that lab analysis should transfer to private sector laboratories in 2006. The status as of December, 2005 is that the PHL will extend its role as the sole lab for ChE monitoring through 2006, however there is no commitment to continue beyond that time. The Scientific and Cholinesterase Monitoring Stakeholder Groups, as well as other commenters have urged that a single lab be used for this program, and recommend that the PHL continue in this role if suitable means can be found to permit this (A primary issue is responsibility for employer occupational safety and health programs. The employer must cover the costs of medical surveillance. A fee for service system would need to be put in place.) This would avoid the risk that changing laboratories might result in less certainty regarding ChE depressions and in other ways adversely affect program performance. In the event that the PHL is not available to continue as the ChE monitoring lab, the following are some aspects of lab performance to be considered in selecting a replacement:

1. Analysis precision and accuracy
2. Analysis timeliness
3. Adherence to protocols
4. Responsiveness to communication needs
5. Logistics of sample transfer
6. Support for sample collection and shipment activities
7. Responsiveness to other program requirements or needs
8. Cost
9. Commitment to continued service beyond 2007

Demonstration of adequate performance or responsiveness in these areas prior to the selection of a new laboratory for the program will be important to assure continued program quality. If a new lab were to be used in 2007, developing a performance record in 2006 for that lab would be important in assuring a good transition.

5. Coordination between this program and the PIRT program: these programs are not closely aligned and would not be expected to recognize the same instances of overexposure. Nevertheless, it is important to identify the separate experiences of both programs and to explicitly comment on how these agree or do not.